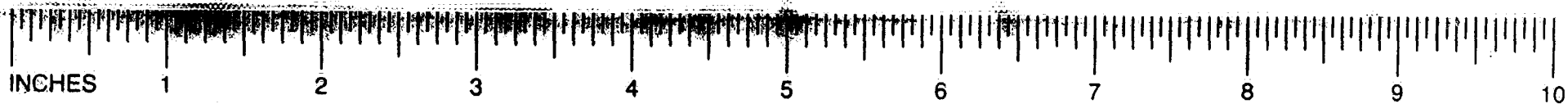


ETS
ISSUE BINDER

ETS AND
RESPIRATORY
DISEASES & CONDITIONS
IN NON-SMOKING
ADULTS & CHILDREN

II

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**ETS AND
RESPIRATORY DISEASES AND CONDITIONS
IN NONSMOKING ADULTS AND CHILDREN**

VOLUME II

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THIS ISSUE BINDER IS INTENDED TO PROVIDE A BASIC,
COMPREHENSIVE REVIEW OF THE SCIENTIFIC LITERATURE
REGARDING A SPECIFIC TOPIC ON ETS AND THE HEALTH OF
NONSMOKERS.

PRIMARY STUDIES AND REVIEWS HAVE BEEN HIGHLIGHTED
TO IDENTIFY (1) USEFUL OR HELPFUL INFORMATION (YELLOW
HIGHLIGHT) AND (2) ADVERSE RESULTS OR OPINIONS (BLUE
HIGHLIGHT).

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INTRODUCTION
ETS AND CHILDHOOD AND ADULT RESPIRATORY DISEASE/SYMPTOMS

This issue binder is designed to provide a comprehensive review of the major literature on environmental tobacco smoke and childhood and adult respiratory disease/symptoms. The book has been divided into subsections: (A) childhood respiratory disease/symptoms; (B) childhood pulmonary function; (C) compromised children such as asthmatics and children with cystic fibrosis; (D) otitis media; (E) adult respiratory disease/symptoms; (F) adult pulmonary function; (G) compromised adults; and (H) confounders.

Each section provides a short introduction to the topic. Major studies are preceded by a short abstract and followed by published critiques of the study. Each of the studies is highlighted to facilitate understanding of the issue: 1) favorable points are highlighted in yellow, and 2) unfavorable points are highlighted in blue. Tables and charts in the notebook are also highlighted in yellow (favorable) and blue (unfavorable).

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STUDY ABSTRACTS

In the majority of cases, the abstract or summary that precedes the individual study is the actual quoted abstract of the article's authors. However, some authors did not present an appropriate summary or abstract in their article. In those cases, a brief summary of the article was prepared. The abstracts and summaries prepared by the individual authors of the studies are designated as "abstracts" and "summaries."

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PARENTAL SMOKING AND COMPROMISED CHILDREN

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COMPROMISED CHILDREN

The literature on environmental tobacco smoke includes a body of research on asthma and the relationship between parental smoking and preexistent disease in children. While only a few studies have been conducted thus far on children with, for example, cystic fibrosis (a genetic disorder whereby lung passages often become blocked by abnormally behaving mucus), there have been numerous studies that have examined asthmatic children and the presence of smokers in the home. The results of the studies have been variable and are subject to the influences of many different confounders such as socioeconomic status, genetic determinants, damp housing, and gas cooking in the home. It is not suprising, therefore, that researchers are inconsistent in their interpretation of the available data on exposure to ETS and childhood asthma. Following is a presentation of the major studies that have examined a possible association of ETS with asthma in children. Also included are the studies available on children with cystic fibrosis.

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RESULTS OF SELECTED STUDIES: COMPROMISED CHILDREN

Leeder, et al., 1976

Reported that episodes of asthma in the first five years of life showed an association with parental history of asthma-wheeze and that there is little relationship between asthma in the first five years of life and other family, social, or environmental factors.

Fergusson, et al., 1985

Reported that maternal smoking increased the risk of lower respiratory infections/symptoms during the child's first two years of life, and that after two years this association seemed to disappear. Also reported that there was no increased risk of asthma or asthma attacks attributable to maternal smoking.

Horwood, et al., 1985

Reported that there was no evidence to suggest that the structure, practices (including parental smoking), or the dynamics of the family played a significant role in the development of childhood asthma.

Murray, et al., 1986

Reported that maternal smoking aggravated symptoms in asthmatic children.

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Anderson, et al., 1987

Reported that sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy, adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks were associated with the development of childhood asthma.

Evans, et al., 1987

Reported that parental smoking increased the number of emergency room visits of children with asthma. The lack of an association between parental smoking and symptoms in asthmatic children caused the authors to question the mechanism whereby parental smoking would increase ER visits.

Toyoshima, et al., 1987

Reported that it was not clear whether parental smoking increased the incidence of asthmatic disease in children.

Kershaw, 1987

The authors conceded that the association observed with parental smoking may reflect a relationship of smoking behaviour to a number of other social factors such as medical care utilization and maternal stress.

Murray, et al., 1988

Reported that paternal smoking, including the number of cigarettes the father smoked at home, had no association with any test results. Maternal smoking in the "wet and cold" season was reported to increase the severity of the child's asthma. There was no association in the "warm and dry" season

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and the severity of the child's asthma. The authors attribute this to increased ventilation in the "warm and dry" season.

Somerville, et al., 1988

Reported a positive association between parental smoking and asthma in girls and a non-significant negative relation between parental smoking and asthma in boys.

Oldigs, et al., 1990

Reported that in children with mild bronchial asthma one hour of passive smoke exposure did not cause airway obstruction or changes in bronchial responsiveness.

Sherman, et al., 1990

Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of childhood asthma.

Weitzman, et al., 1990

The authors concede that the estimate of children's exposure to cigarette smoke is "crude", based on parent reporting of smoking during pregnancy.

Rubin, 1990

Reported an association between parental smoking and the severity of cystic fibrosis in children. However, the authors conceded that it could not be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children.

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Gilljam, et al., 1990

Reported that there was no statistical difference in clinical status or pulmonary function between children with cystic fibrosis from smoking and nonsmoking families. For patients with higher levels of physical activity, parental smoking appeared to matter less.

Young, et al., 1991

Reported that parental smoking may contribute to a higher level of airway responsiveness early in the child's life. The authors conceded that they did not report the actual amount of parental smoking due to the inaccuracies of parental reporting.

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Leeder, S.R., Corkhill, R.T., Irwig, L.M., Holland, W.W., Colley, J.R.T. "Influence of family factors on asthma and wheezing during the first five years of life" Brit J. prev. soc. Med. 30: 213-218, 1976.

ABSTRACT. Family factors associated with the incidence of asthma and wheezing during childhood have been studied in a cohort of over 2000 children who, together with their families, were followed-up for five years. Episodes of wheezing not regarded by the parents as asthma had a different pattern of association with family factors to that found for asthma. The outcome of the two conditions in terms of ventilatory function at the age of five years was also different, in that children with a history of asthma had a lower peak expiratory flow rate than did children with a history of non-asthmatic wheezing.

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Influence of family factors on asthma and wheezing during the first five years of life

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Leeder, S. R., Corkhill, R. T., Irwig, L. M., Holland, W. W., and Colley, J. R. T. (1976). *British Journal of Preventive and Social Medicine*, 30, 213-218. Influence of family factors on asthma and wheezing during the first five years of life. Family factors associated with the incidence of asthma and wheezing during childhood have been studied in a cohort of over 2000 children who, together with their families, were followed-up for five years. Episodes of wheezing not regarded by the parents as asthma had a different pattern of association with family factors to that found for asthma. The outcome of the two conditions in terms of ventilatory function at the age of five years was also different, in that children with a history of asthma had a lower peak expiratory flow rate than did children with a history of non-asthmatic wheezing.

Attacks of wheezing are common events in childhood in the United Kingdom. Two studies showed that some 20% of children received attention from their general practitioner for at least one episode of wheezing during their first decade (Fry, 1961; Goodall, 1958). The relationship between attacks of wheezing accompanying acute lower respiratory infection, sometimes termed wheezy bronchitis, and wheezing precipitated by allergens, emotional stress, or exercise is particularly difficult to define (*British Medical Journal*, 1973; Gordis, 1973). It is likely that in some cases episodes of wheezing mark the beginning of chronic bronchial asthma (Williams and McNicol, 1969; Gandevia *et al.*, 1973). In this paper we report observations on different family factors associated either with episodes of wheezing considered by parents not to be asthma, and with what the parents termed asthma, in over 2000 children who were studied, together with their families, until the children were five years old. We reasoned that if all attacks of wheezing were in

reality mild attacks of asthma, they would be associated with the same family factors as frank asthma.

METHODS AND MATERIALS

The methods and materials pertaining to this study are described in the preceding paper.

RESULTS

By the age of five years, one or more episodes of asthma had been reported in 3.4% of boys and 2.9% of girls. Wheezy, whistling, or chesty episodes without asthma were reported in 22.5% of boys and 20.7% of girls.

Episodes of wheezing rather than asthma were associated with a history of bronchitis or pneumonia in children during their first year of life, 41.2% of children with a history of bronchitis or pneumonia in the first year subsequently suffered from wheezing, compared with 19.2% of children without bronchitis or pneumonia (Table I: relative risk for wheeze is 2.15). Asthma was not so strongly associated with bronchitis or pneumonia in the first year, 4.3% of children with this history suffered from subsequent

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TABLE I
INCIDENCE PER 100 INDEX CHILDREN OF WHEEZING* IN FIRST FIVE YEARS OF LIFE BY BRONCHITIS OR PNEUMONIA
IN FIRST YEAR, AND BY PARENTAL ASTHMA-WHEEZE

		Parental Asthma-Wheeze			
		Neither	One	Both	Total
Bronchitis or pneumonia in the first year	No	17.7 (1333)	24.2 (421)	16.0 (50)	19.2 (1804)
	Yes	37.7 (138)	46.8 (77)	44.4 (18)	41.2 (233)
	Total	19.6 (1471)	27.7 (498)	23.5 (68)	21.7 (2037)†

Populations in parentheses.

*Wheezing excludes children who had asthma.

†Total excludes 96 index children with missing first, third, fourth, and fifth year data and an additional 16 with missing initial data on parent pairs.

asthma, compared with 3.0% of children without this history (Table II: relative risk for asthma is 1.41). In children with one parent with a history of asthma-wheeze, the incidence of asthma was 5.4% compared with 2.5% of children whose parents were both free of asthma-wheeze. The incidence of wheezing was also higher in children with one parent with a history of asthma-wheeze (27.7%) compared with children of parents without such a history (19.6%). However, the risk was no greater, and sometimes less, if both parents had asthma-wheeze. This inconsistent trend may partly be a consequence of some rates being based on small numbers (Tables I and II). There was no consistent relationship between smoking and cough-phlegm in the parents and asthma in the children, although conclusions are limited once more by small numbers of children with asthma in some cells (Table III). By contrast, wheezing was consistently more common in children when their parents smoked or suffered from cough-phlegm (Table IV).

Asthma was reported more commonly in children of parents in the upper social than in children of lower social class parents (Table V). However, the rates were based on small numbers and the social class gradients were not wholly consistent at all ages; for example, the lowest incidence occurred in children up to the age of three years with parents from social class III. Wheezing was more common in children of lower social class parents. Area of residence had no influence on the incidence of asthma or wheezing.

As some of the family factors examined in the preceding tables were themselves interrelated, it was difficult to assess the influence of each individual factor upon the incidence of asthma or wheezing in the index children. To investigate these relationships, two logistic models were fitted to the data, one with the incidence of asthma in the index children as the outcome variable, and the other with the incidence of wheezing as the outcome variable. The independent variables included in both models were parental

TABLE II
INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA* IN FIRST FIVE YEARS OF LIFE BY BRONCHITIS OR PNEUMONIA
IN FIRST YEAR, AND BY PARENTAL ASTHMA-WHEEZE

		Parental Asthma-Wheeze			
		Neither	One	Both	Total
Bronchitis or pneumonia in the first year	No	2.3 (1333)	5.5 (421)	2.0 (50)	3.0 (1804)
	Yes	3.6 (138)	5.2 (77)	3.6 (18)	4.3 (233)
	Total	2.5 (1471)	5.4 (498)	2.9 (68)	3.2 (2037)†

Populations in parentheses.

*Asthma includes children who may have wheezed as well.

†Total excludes 96 index children with missing first, third, fourth and fifth year data and an additional 16 with missing initial data on parent pairs.

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TABLE III
INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA* IN FIRST FIVE YEARS BY PARENTAL COUGH-PHLEGM AND SMOKING HABITS

Parents Smoking:	Parental Cough-Phlegm (During Period First to Fifth Year)			
	Neither Parent Ever Positive	Symptom Changed in One or Both Parents	One or Both Parents Always Positive	Total
Neither	2.9 (307)	1.5 (134)	— (4)	2.5 (445)
Habit changed in one or both	3.9 (279)	3.3 (299)	— (27)	3.5 (605)
One parent consistently smoking	3.3 (184)	2.2 (228)	5.8 (52)	3.0 (464)
Both smokers	1.1 (90)	4.0 (249)	8.0 (25)	3.6 (364)
Total	3.1 (860)	3.0 (910)	4.6 (108)	3.1 (1878)†

Populations in parentheses.

*Asthma includes children who may have wheezed as well.

†Total excludes 72 index children with missing third, fourth, and fifth year data and an additional 199 with missing first to fifth year data on parent pairs.

‡Considered over the full five years of the study.

TABLE IV
INCIDENCE PER 100 INDEX CHILDREN OF WHEEZING* IN FIRST FIVE YEARS BY PARENTAL COUGH-PHLEGM AND SMOKING HABITS

Parents Smoking	Parental Cough-Phlegm (During Period First to Fifth Year)			
	Neither Parent Ever Positive	Symptom Changed in One or Both Parents	One or Both Parents Always Positive	Total
Neither	16.6 (307)	27.6 (134)	25.0 (4)	20.0 (445)
Habit changed in one or both	13.3 (279)	26.1 (299)	29.6 (27)	20.3 (605)
One parent consistently smoking	11.4 (184)	28.1 (228)	23.1 (52)	20.9 (464)
Both smokers	21.1 (90)	27.3 (249)	36.0 (25)	26.4 (364)
Total	14.9 (860)	27.1 (910)	27.8 (108)	21.6 (1878)†

Populations in parentheses.

*Wheezing excludes children who had asthma.

†Total excludes 72 index children with missing third, fourth, and fifth year data and an additional 199 with missing first to fifth year data on parent pairs.

TABLE V
INCIDENCE PER 100 INDEX CHILDREN OF ASTHMA OR WHEEZING* DURING FIRST FIVE YEARS BY PARENTAL SOCIAL CLASS AT FIFTH YEAR

Illness in Children of Parents According to Social Class	Age in Years						Population
	By Age Three		By Age Four		By Age Five		
	Asthma	Wheezing	Asthma	Wheezing	Asthma	Wheezing	
Social class I and II	2.0	17.2	3.1	19.2	4.0	20.8	751
III	1.0	20.2	2.1	22.3	2.7	23.5	997
IV and V	1.4	21.2	1.8	24.5	2.5	27.3	278
Unknown	3.9	13.7	3.9	17.7	3.9	17.7	51
Total	1.5	19.1	2.5	21.3	3.2	22.9	2077†

*Asthma includes children who may have wheezed as well; wheezing excludes children who had asthma.

†Total excludes 72 index children with missing third, fourth, and fifth year data.

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smoking, parental cough-phlegm, parental asthma-wheeze, number of siblings and their history of bronchitis or pneumonia and of asthma-wheeze, the sex of the index child, history of bronchitis or pneumonia in the first year of life, social class of the father when the child was aged five years, and area of residence.

In asthma, a history of parental asthma-wheeze was the only statistically significant factor. However, with wheezing, parental cough-phlegm and bronchitis or pneumonia during the first year of life of the child were both found to be statistically significant. The model was then refitted with these two factors alone as independent variables. The crude and adjusted incidence rates using this model are presented in

Table VI, which shows that bronchitis or pneumonia during the first year of life had the greater effect upon the incidence of wheezing.

The influence of a history of asthma or wheezing on peak expiratory flow rate at five years was examined in those children for whom these data were available (Table VII). Peak expiratory flow rates were adjusted for differences in sitting height at age five years. Children with a history of both asthma and bronchitis or pneumonia had a significantly lower mean peak expiratory flow rate than those with a history of bronchitis or pneumonia alone; a difference of 17.4% ($P < 0.001$). Mean peak flow rates in children with a history of wheezing and bronchitis or pneumonia did not differ significantly from those

TABLE VI
CRUDE AND ADJUSTED INCIDENCE RATES PER 100 CHILDREN OF WHEEZING* FOR LEVELS OF EACH FACTOR WITH ESTIMATES OF THEIR EFFECTS

Factor and Level	Crude Incidence Rate	Adjusted Incidence Rate	Significance of the Factor in the Model		
			χ^2	df	P
Parental cough-phlegm					
Neither	17.7 (1263)	17.6	22.69	2	< 0.0005
One	27.2 (670)	26.3			
Both	34.6 (78)	30.3			
Bronchitis or pneumonia in the first year					
No	18.9 (1781)	18.8	43.63	1	< 0.0005
Yes	41.3 (230)	39.4			
Total	21.5 (2011)†	—	—	—	—

Populations in parentheses.

*Wheezing excludes children who had asthma.

†Total excludes 96 index children with missing first, third, fourth, and fifth year data and an additional 42 with missing initial or first year data on parent pairs.

TABLE VII
MEAN PEAK EXPIRATORY FLOW RATES IN CHILDREN AGED FIVE YEARS, BY HISTORY OF ASTHMA, WHEEZING, BRONCHITIS, OR PNEUMONIA

Symptom Group	Mean PEFR†	Population	Standard Error of the Mean	Significance of Difference Between Means of Groups With and Without Symptoms	
				t	P
Nil	151.5	292	1.5	0.51 3.95 2.34 2.38	0.6 < P < 0.7 P < 0.001 0.01 < P < 0.02 0.01 < P < 0.02
Asthma without bronchitis or pneumonia	149.2	40	4.1		
Wheezing without bronchitis or pneumonia	118.6	10	8.2		
Asthma with bronchitis or pneumonia	140.3	33	4.3		
Wheezing with bronchitis or pneumonia	143.5	76	3.0		
Total	—	454†	—	—	—

*Asthma includes children who may have wheezed as well; wheezing excludes children who had asthma.

†Total excludes 4 index children with successful flow rate measurements at age five years but with missing first to fourth year data. The remaining 1691 children were not measured at age five years.

‡Litres/min, adjusted for sitting height at age five years.

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with a history of bronchitis or pneumonia alone. The 40 children with a history of wheezing alone had peak flow rates similar to those of children without a history of asthma, wheezing, bronchitis, or pneumonia.

DISCUSSION

Episodes of wheezing, 'whistling' or 'chestiness' not termed asthma by parents occurred much more commonly (in 21.7% of children) than asthma (3.2%) by the age of five years. Wheezing episodes were closely associated with bronchitis and pneumonia occurring during the first year. Wheezing was also associated with parental cough-phlegm and smoking as was bronchitis or pneumonia in the first year (Leeder *et al.*, 1976). This suggests that at least some of the environmental factors associated with bronchitis or pneumonia may also be important in the development of wheezing episodes in later childhood. Alternatively, genetic factors associated with bronchitis or pneumonia in the first year may also predispose to wheezing in later childhood. Damage to airways caused by bronchitis or pneumonia in early childhood may also make children more liable to wheeze subsequently.

While episodes of asthma in the first five years of life also showed an association with parental history of asthma-wheeze (as did episodes of wheezing not termed asthma) there is little relationship between asthma in the first five years and other family, social, or environmental factors.

In this study, the parents' account of asthma and wheezing in their children was used to define these illnesses. Despite the uncertainties implicit in using parentally reported data, asthma and wheezing were, as discussed, associated with different family factors. Also, the effects of asthma and wheezing on peak expiratory flow rates at the age of five years were different. Children with a history of asthma had lower peak expiratory flow rates at the age of five than the children with a history of wheezing alone. In asthma adequate treatment can often reverse much of the airways obstruction. The low peak expiratory flow rate at the age of five we found in children with a history of asthma may indicate the need for vigorous bronchodilator therapy. Alternatively, this deficit may reflect irreversible airways obstruction (Cade and Pain, 1973). More concerted treatment in the first five years of life may have prevented its development. Whatever the potential for the reversal of the decreased peak expiratory flow rate found in children with a history of asthma, it appears that the parents' account

differentiated between important and unimportant illness, according to whether they termed it asthma or wheezing.

The incidence rates for asthma and wheezing obtained in studies of children clearly depend upon how these two conditions are defined and the populations in which surveys are conducted. In a study of Kent schoolchildren, using similar methods to those used in this study, Hamman, Halil, and Holland (1975), found comparable rates of asthma by the age of 11 years to those that we found by the age of five years. Similar incidence rates for asthma were found in a study of schoolchildren in Birmingham (Smith, 1961).

Asthma was reported more commonly in children of upper class parents, whereas the reverse was true of wheezing. These social class trends could reflect differences in reporting behaviour among parents of different social classes. More parents in social classes I and II may report asthma rather than wheezing episodes when confronted with essentially the same illness in their children. Alternatively, there could be a real difference in the social class distribution of asthma. Hamman *et al.* (1975) found a similar trend to the one described in this paper while Dawson *et al.* (1969) in a study in Aberdeen, Scotland, found a social class trend in asthma incidence contrary to ours.

The incidence of wheezing may prove to be more modifiable than that of asthma by changing environmental factors, as attacks of wheezing were closely associated with bronchitis and pneumonia during the first year of life. Bronchitis and pneumonia in the first year have, in turn, been shown to be associated with such factors as parental smoking habits (Colley, Holland, and Corkhill, 1974). Thus, efforts to prevent bronchitis and pneumonia during the first year of life may also reduce the incidence of wheezing and of other chest illnesses in later childhood.

The syndromes of lower respiratory illness in childhood remain poorly defined and it is clear that the precision of diagnosis of these illnesses requires improvement before more effective treatment can be given to the children who require it. On the basis of the epidemiological evidence presented here, it seems most unlikely that all forms of the more frequent lower respiratory illness in childhood are simply manifestations of a single common disorder. There may well be common features in aetiology and natural history between conditions such as asthma and bronchitis, but this is not a good reason to use these terms interchangeably. This is especially important when strategies for prevention of one or other condition are being considered.

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ABSTRACT. Data from two random population surveys are used to assess the relationship between parental smoking and the prevalence of asthma in children aged 0-17. Data from a 1977 Midwestern urbanized county indicate that, if mothers smoked, the prevalence of parent reported asthma increased from 5.0 per cent to 7.7 per cent (estimated relative risk of 1.5) and the prevalence of functionally impairing asthma increased from 1.1 per cent to 2.2 per cent (relative risk of 2.0). In a more rural Eastern county in 1980, a lower overall prevalence of asthma was noted. However, similar estimated relative risks of asthma (1.8) and functionally impairing asthma (2.4) were found to be associated with maternal smoking. Inconsistent relationships were found between the estimated prevalence of asthma and paternal smoking. When multivariate controls were introduced, the relationships between maternal smoking and asthma persisted. Estimated attributable risks indicate that between 18 per cent and 34 per cent of the asthma reported in these samples can be attributed to maternal smoking. Implications of these findings for primary care physicians are discussed.

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Parental Smoking and the Risk of Childhood Asthma

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Abstract: Data from two random population surveys are used to assess the relationship between parental smoking and the prevalence of asthma in children aged 0-17. Data from a 1977 Midwestern urbanized county indicate that, if mothers smoked, the prevalence of parent reported asthma increased from 5.0 per cent to 7.7 per cent (estimated relative risk of 1.5), and the prevalence of functionally impairing asthma increased from 1.1 per cent to 2.2 per cent (relative risk of 2.0). In a more rural Eastern county in 1980, a lower overall prevalence of asthma was noted. However, similar estimated relative risks of asthma

(1.8) and functionally impairing asthma (2.4) were found to be associated with maternal smoking. Inconsistent relationships were found between the estimated prevalence of asthma and paternal smoking. When multivariate controls were introduced, the relationships between maternal smoking and asthma persisted. Estimated attributable risks indicate that between 18 per cent and 34 per cent of the asthma reported in these samples can be attributed to maternal smoking. Implications of these findings for primary care physicians are discussed. (*Am J Public Health* 1982; 72:574-579.)

Introduction

The health hazards of cigarette smoking have been well documented and widely accepted.¹⁻⁴ Recently attention has focused on the relationship between exposure to cigarette smoke and the health of nonsmokers. Several studies⁵⁻¹⁰ have noted the substantial effects of cigarette smoke on "indoor pollution." Repace and Lowrey, for example, conclude that "levels of respirable suspended particulates in places where tobacco is smoked greatly exceed levels found in smoke-free environments, outdoors, and vehicles on busy commuter highways."⁶ White and Froeb found that nonsmokers who were chronically exposed to cigarette smoke in the workplace had levels of pulmonary function similar to that of light smokers and lower than nonsmokers in a smoke-free environment.⁷ Hirayama found a significantly increased risk of lung cancer for nonsmoking wives of heavy smokers.⁸

The present study focuses upon parental smoking and childhood asthma. Asthma is one of the leading causes of chronic illness in children; children with asthma experience a characteristic hyperreactivity of the airways to a variety of environmental factors, including irritants such as tobacco smoke.¹¹ Studies have noted relationships between air pollution and the onset of asthma attacks,^{12,13} but no significant relationships between parental smoking and the prevalence

of asthma have been reported. Several studies have noted relationships between parental smoking and acute respiratory illness in children,¹⁴⁻¹⁷ and the results have been fairly consistent. A significant dose-response relationship was found between parental smoking and reported bronchitis and pneumonia in infants by Harlap and Davies¹⁸ and Colley, *et al.*¹⁹ One study found a dose-response relationship between parental smoking and adenoidectomy and tonsillectomy in children,²⁰ and another demonstrated a significant relationship to pulmonary function in children.²¹ O'Connell and Logan examined clinical records of asthmatic and non-asthmatic children; they found only a small difference in the incidence of parental smoking, but a majority of the parents of their asthmatic children reported that cigarette smoke aggravated the asthma, and elimination of smoking generally led to improvement.²²

The analyses described below report on the results of two population surveys carried out in 1977 and 1980 in two locations across the United States.

Materials and Methods

A random household health survey was conducted in Genesee County, Michigan in 1977. Information upon 3,072 children (aged 0-17) and their households was obtained from an adult family member, usually the mother. The response rate was 81 per cent. The city of Flint, Michigan (population 165,000 in 1977) is an industrial city in the southeastern region of the state of Michigan. Flint and the surrounding Genesee County (total population 450,000) are heavily dependent upon automobile-related industries for employment.

Berkshire County, Massachusetts (population in 1980 of 146,000) is a relatively rural county which forms the western

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boundary of the State of Massachusetts. The largest city is Pittsfield (1980 population of 53,000). A randomly dialed telephone survey of households with children (aged 0-17) was conducted in 1980, using many identical questions from the Genesee County survey. The response rate for this survey was 81 per cent; information upon 894 children was available for analysis.

The smoking habits of mothers and fathers in the households were assessed using identical questions in both the Michigan and Massachusetts surveys: the respondent was asked whether or not each household member smoked cigarettes, and if so, how much. For analysis, mothers and fathers were classified as either smokers or nonsmokers. The samples were too small to reliably estimate relations involving different amounts of smoking.²¹

The presence of asthma among children was assessed using a 22-item chronic condition checklist in the Genesee County survey, and a 21-item checklist in the Berkshire County survey. In Genesee County, the parents were handed a card listing all of the conditions (Appendix A). The same checklist except for the item "bronchitis," was read to respondents in the Berkshire County survey. The questions asking about asthma, hayfever, and any other kind of allergy were exactly the same as questions asked in earlier surveys in Rochester, New York,²² and in the National Health Examination Survey,²³ and are very similar to checklists used in the National Health Interview Survey.²⁴

If the parent (usually the mother) confirmed that the child had a certain condition, they were asked, "Does it affect his/her ability to attend school or do any of the things a child his/her age usually does?" "Yes" responses to this question were coded as indicating a functionally impairing condition. Parents were also asked whether a doctor had been seen about this condition.

A number of studies have indicated that parent reports in general overestimate the prevalence of clinically diagnosed chronic conditions. Others have noted, however, that overreporting tends to decline with the reported severity of the condition; i.e., more severe conditions, which have a greater impact upon the individual, tend to be more completely reported.^{25,27}

For example, a household survey in Alamance County, North Carolina resulted in an estimated prevalence of a variety of respiratory conditions in children under age 21 of 16.3 per cent. In contrast, a clinically validated estimate (moderate and severe cases only) of 2.9 per cent was obtained.²⁸ Another household survey in Rochester, New York (utilizing exactly the same questions as the present study) produced a prevalence estimate of 3.2 per cent of asthma in children 0-17 years of age. Follow-up interviews of children aged 6-17 resulted in a validated estimate of 9 per cent prevalence of asthma.²⁴ These estimates are also consistent with validated estimates obtained in a population study on the Isle of Wight in England for 10-12 year olds; a prevalence of asthma of 2.3 per cent was estimated; when

only chronically handicapping asthma was considered, this estimate was halved.²⁹

In summary, significant errors in the reporting of childhood asthma have been found in studies utilizing parent interviews, although there is evidence that these errors tend to decrease if the severity of the condition is taken into account. It is important to note, however, that these errors will not bias relationships estimated between parental smoking and asthma unless asthma misreporting is related to parental smoking.³⁰ Tests for such systematic bias are reported below.

Results

Overall, the estimated prevalence of asthma in these samples appears similar to that found in a national sample of children in the 1963-1965 National Health Examination Survey,³² 5.3 per cent among children aged 6-11. The corresponding estimates in Genesee County (1977) and Berkshire County (1980) are 6.5 per cent and 2.6 per cent, respectively. The lower estimate for Berkshire County also corresponds to relationships reported from National Health Interview Survey data in 1970, which noted a decreased prevalence of asthma among children living in rural areas, as opposed to urban areas.³³

The estimated prevalence of functionally impairing asthma in the present samples (1.5 per cent, .8 per cent) is also comparable to the clinically validated prevalence estimates noted above; again, a higher prevalence is found in the urban sample.

Validation of these parent reports is made possible through use of other questions in the household surveys. In the Michigan survey, if a child was noted as having asthma, parents were asked if they had "been to a doctor about this?" All of the parents who reported a child with asthma said they had been to a doctor about the child's condition. In the Massachusetts survey, another question asked for all children was the following: "Today or yesterday has (child's name) taken or used any medicine, salves, or pills that were prescribed by a doctor?" Of the 29 children in this sample reported by parents as asthmatic, seven were reported to be taking asthma medication regularly; the medication was specified in six of these cases, and no children without asthma were reported as receiving asthma medication. Of the seven children in the sample identified as having functionally impairing asthma, four were reported to be taking medication for the condition. The answers to both of these survey questions suggest that the parent reports are valid

³⁰In regression analysis, it is well known that random error in the dependent variable will not bias estimates of regression coefficients, although the explained variance will decrease.³¹ The analogous corollary for the logistic regressions used later is derived from the well-known fact that odds ratios that characterize a cross-classification are invariant to multiplication of rows or columns by a constant.³² Thus, if both smoking and nonsmoking mothers overreport asthma by a proportionate amount, estimates of odds ratios will not be affected.

²¹Of the mothers who smoked, 61 per cent in the Michigan sample and 56 per cent in the Massachusetts sample reported smoking a half to one pack per day.

TABLE 1—Estimated Prevalence of Asthma in Children, by Smoking of Mothers; Genesee County, Michigan (1977) and Berkshire County, Massachusetts (1980).

Site/Condition	Maternal Yes	Smoking No	Estimated Relative Risk	χ^2	p-value (one-tailed)
Genesee County, MI (N)	(1,255) ^a	(1,817)			
Asthma	7.7	5.0	1.53	9.1	.001
Functionally Impairing Asthma	2.2	1.1	1.95	5.4	.01
Berkshire County, MA (N)	(330)	(564)			
Asthma	4.5	2.5	1.83	2.8	.05
Functionally Impairing Asthma	1.2	0.5	2.28	1.2	.13

^aSample sizes are given in parentheses.

and again indicate that parent reporting likely increases in accuracy as the severity of the condition increases.

In the Genesee County, Michigan sample, 41 per cent of the children aged 0-17 had mothers who smoked. The estimated prevalence of asthma was 7.7 per cent for children of smoking mothers, and 5 per cent for children of nonsmoking mothers (Table 1). These differences are statistically significant at $p = .001$. A similar relationship is also noted in this Table between maternal smoking and the estimated prevalence of functionally impairing asthma, 4.1 per cent versus 2.2 per cent, indicating a doubling in the risk among children of smoking mothers.

Data from the more rural Berkshire County sample produced similar estimates of relative risk, although the significance levels were lower due to the smaller sample size. Thirty-seven per cent of the children aged 0-17 in this sample had a mother who smoked. The estimated prevalence of asthma symptoms increased from 2.5 per cent to 4.5 per cent among children with mothers that smoked, and the estimated prevalence of functionally impairing asthma doubled (from .5 per cent to 1.2 per cent).

***All tests of the smoking/asthma relationship will be one-tailed tests; other tests will be two-tailed. It should also be noted that the sample in fact consists of data upon clusters of children; thus, even though households were selected randomly, some design effect is introduced into the sample. We estimate from the present samples that ρ_{hh} , the intraclass correlation coefficient which measures this tendency towards homogeneity within clusters, is .16 for asthma, and .21 for function impairing asthma. The effect of this clustering is to reduce the precision of the survey estimates. For example, in the Genesee County sample a 95 per cent confidence interval around the proportion of children reported as asthmatic by mothers that do not smoke can be estimated at 4-6 per cent if the effects of clustering are ignored. If this design effect is taken into account, the 95 per cent confidence interval becomes 3.8-6.2 per cent. Others have found that design effects are less pronounced for regression coefficients than for estimates of means and proportions.¹⁴ Regressions were run based upon households which predicted the proportion of children in a household with asthma, controlling for family size and other variables noted later. These results were consistent with results presented later, and thus indicate no significant consequences of this design effect.

No significant differences in the relationships between maternal smoking and asthma, and maternal smoking and functionally impairing asthma were found between the two geographic areas. Log-linear models were fitted, testing for this three-way interaction, and no significant differences emerged. Thus, data from the two sites were pooled, using a variant of the Mantel-Haenszel procedure.¹⁵ This analysis, as expected, results in slightly higher levels of statistical significance of the asthma and smoking relationships.

Other Explanatory Variables

The relationship of paternal smoking to childhood asthma was also explored in both samples, but the results were inconsistent. In Genesee County, Michigan, significant relationships were found between paternal smoking and the prevalence of childhood asthma but not of functionally impairing asthma. In Berkshire County, no significant relationships between paternal smoking and the risk of asthma or functionally impairing asthma were observed.

Parents who smoke could conceivably be over-sensitized to the effects of their smoking, and thus could over-report conditions in their children. This possible bias in symptom reporting was explored by looking at the relationship between maternal and paternal smoking and other chronic conditions¹⁶ for which respiratory symptoms might appear. No significant relationships were found.¹⁷

Multivariate logistic regression^{18,19} were estimated which predicted asthma and functionally impairing asthma among children from mothers' smoking habits, as well as from the smoking habits of fathers, whether the child had hayfever or any other allergies, and socioeconomic and demographic characteristics of the family and child. The coefficient estimates from these equations estimated from

¹⁶These conditions included hayfever and any other allergies.

^{18,19}These logistic regressions estimate linear associations between the predictor variables and the logarithm of the odds for asthma. They were estimated using MMLA, a computer program which produces maximum likelihood estimates, written by W. W. Hauck, Illinois Cancer Council, Chicago, Illinois.

TABLE 2—Coefficient Estimates from Logistic Regressions Predicting Asthma and Functionally Impairing Asthma in Children 0-17, Genesee County, MI, 1977

Variable	Equation Predicting Asthma			Equation Predicting Functionally Impairing Asthma		
	Coefficient Estimate	t-Statistic	Odds-ratio	Coefficient Estimate	t-Statistic	Odds-ratio
Mother Smokes (Yes = 1) [†]	.401	2.45**	1.49	.613	1.94*	1.85
Father Smokes (Yes = 1)	.398	2.40*	1.49	.076	.24	1.08
Age of Child (1 ≤ 5)	-.358	-1.79	.70	-.299	-.78	.74
Sex of Child (1 = male)	.115	.73	1.12	-.236	-.79	.79
Income of Family (1 = poverty; 2 = near poverty; 3 = higher)	.028	.20	1.03	-.077	-.33	.93
Mother's Education	-.226	-2.32*	.80	-.488	-2.44*	.61
Child has Allergies (Yes = 1)	1.169	6.44**	3.22	1.230	3.70**	3.42
Child has Hayfever (Yes = 1)	1.686	8.51**	5.40	1.585	4.36**	4.88

*Significant at $p = .05$ **Significant at $p = .01$ [†]Other responses coded as "0" if first category is "1"

the Genesee County data are displayed in Table 2 above. A variety of other variables are not included in this Table because they did not add any explanatory power to these equations. These include the number of persons in the household, race, environmental deficiencies observed near the home (available only in the Genesee County sample), number of rooms in the house, and mother's work status.

The most important result of this analysis is that the addition of all of these control variables did not substantially alter the estimated relationships between maternal smoking and the prevalence of asthma and functionally impairing asthma. The estimated odds-ratios which describe these relationships, controlling for the variables, are only attenuated slightly from "unadjusted" estimated odds ratios derived from Table 1.^{‡‡} For example, the odds-ratio relating asthma and maternal smoking changes from 1.57 to 1.49; the corresponding change for the functionally impairing asthma odds ratio is from 1.98 to 1.85. Similar equations were estimated for the Berkshire County sample, resulting in similar estimates of the relationship between maternal smoking and asthma. The smaller sample size from this site, however, resulted in lower levels of statistical significance. These analyses also confirmed the fact that paternal smoking did not in general predict chronic respiratory problems once maternal smoking was controlled.

Bronchitis was included as one of the items on the chronic condition checklist in the Genesee County sample, and significant relationships were found between the prevalence of bronchitis and maternal smoking ($p < .001$; estimated relative risk of 1.3). However, no association with functionally impairing bronchitis was observed, and no significant association between bronchitis and paternal smoking was found. These relationships suggest another

effect of maternal smoking, similar to the known effects of individual smoking upon the production of bronchitis in the smoker.[§] This relationship may also reflect the fact that some children with asthma are misdiagnosed as having chronic bronchitis.[¶] The converse, however, could also be true. We reestimated the equations described in Table 2 including an additional control variable indicating whether the child had bronchitis or not. While the bronchitis variable was significant in these equations, maternal smoking was still significantly related to both asthma and functionally impairing asthma, and the coefficient estimates were only slightly attenuated (to 1.42 and 1.70).

One other variable which could have important implications is the presence of asthma in parents, but we believe that this variable could have an attenuating effect upon the present relationships. We assume that parents with a history of asthma have a smaller probability of taking up smoking. Thus, there could be a selection of "non-asthmatic" parents into the group of smokers, and subsequently a selection of "non-asthmatic" children to smoking parents, a situation that would result in an attenuated relationship between parental smoking and childhood asthma.

Estimates of Attributable Risk

The significance of these estimated relationships for both medical practice and public health are strongly conditioned by the proportion of mothers that smoke; because more than one-third of mothers in both of these samples smoke, the estimated attributable risks[§] associated with maternal smoking are substantial.[¶] The estimates of relative risk in Table 1 indicate that 18 per cent and 23 per cent, respectively of asthma in children in the two sites may be

^{‡‡}In the present situation, the odds ratio closely approximates the estimated relative risk.

[§]Attributable risk can be defined as the "maximum proportion of a disease that can be attributed to a characteristic or etiological factor."[¶]

attributed to maternal smoking, and 28 per cent and 34 per cent respectively of functionally impairing asthma in the two populations can be attributed to maternal smoking.

We have already indicated above that the estimated relative risks associated with maternal smoking are somewhat attenuated as control variables are introduced into the logistic regressions; if these estimates are used in the calculations, slightly smaller attributable risks result (e.g., 17 per cent and 26 per cent rather than 18 per cent and 28 per cent).

Because of the small numbers of conditions reported, the 95 per cent confidence intervals around these estimates are necessarily large; for example, the confidence interval around the estimated percentage of asthma in Genesee County, Michigan, attributable to maternal smoking ranges from 5 per cent to 29 per cent. In spite of this imprecision, the similarity of the estimated attributable risks in the two different populations tends to validate the estimates. Other validations are still needed; however, ideally using more refined measures of both the presence of asthma, the level of functional impairment involved, and the actual air pollution which may be attributed to maternal and paternal smoking.

Smoking and Disability Days

Because other studies have reported relationships between acute illness and parental smoking¹⁴⁻¹⁶ and substantial relationships are reported here between asthma and maternal smoking, an obvious question to be addressed is the extent to which the relationships between acute illness and maternal smoking may be due in part or in whole to the relationships estimated here between chronic illnesses such as asthma and bronchitis and maternal smoking. Maternal smoking and the presence of asthma and bronchitis in the Genesee County sample were all associated with the likelihood of a disability day in the past two weeks. When the presence of asthma and bronchitis was controlled, maternal smoking was still significantly ($p = .04$) related to the odds of a disability day, although the magnitude of the estimated relationships was reduced; e.g., the estimated odds-ratio changed from 1.46 to 1.29 when these controls were introduced. Thus, it appears that the relationships estimated above between maternal smoking and the prevalence of chronic respiratory conditions do not account for all of the often reported relationships between parental smoking and acute respiratory illnesses in children.

Discussion

It is useful to conceptually distinguish three possible roles by which an exogenous factor like tobacco smoke might play a role in the pathogenesis of asthma. Such a factor

"... might be responsible for the inception of asthma by inducing a state of hyperreactivity in the bronchi. Second, it might maintain and reinforce hyperreactivity. Third, it might provoke the expression of hyperreactivity, giving rise to clinically recognizable attacks of asthma."

While the present data do not shed light on the precise role of maternal smoking in the development of childhood asthma,

the analyses clearly indicate an influence controlling for other known factors such as hayfever and allergies.¹⁷ Although estimates of attributable risk should be interpreted with these comments in mind, the present data suggest that maternal smoking can be considered an important factor in the occurrence of childhood asthma.

These data can also be considered as another illustration of the extent to which indoor air pollution is a significant determinant of individual health status. As current energy conservation measures in the United States reduce the flow of air through households, the consequences of indoor pollution due to cigarette smoking could certainly increase in magnitude.

The findings from this study suggest that an opportunity exists for health care providers to help prevent asthma in children, and to reduce the level of functional impairment of asthmatic children. One strategy would be to encourage smoking mothers of children with clinically diagnosed asthma to quit smoking. Some effective therapies have been devised to help smokers end their habit,¹⁸ and referrals to such programs could be arranged.

A number of current pediatric texts do not mention such an approach to treating the asthmatic child.¹⁹ Evaluations of the possible efficacy of these interventions in reducing the prevalence of asthma and functionally impairing asthma could add significantly to current knowledge.

A broader preventive strategy could involve encouraging the reduction or elimination of maternal smoking among families with a history of allergies. Such families have a greater risk of producing allergic children. This approach parallels the commonly accepted practice of avoidance therapy with household pets for allergic families.²⁰ There are also substantial benefits to be gained by the mothers themselves if these interventions are successful.

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APPENDIX A

Checklist of Chronic Conditions and Impairments:

- (a) Asthma
- (b) Hay Fever
- (c) Any other kind of allergy
- (d) Any trouble with his/her kidneys
- (e) Anything wrong with his/her heart
- (f) Any difficulty hearing
- (g) Any difficulty seeing (even with glasses)
- (h) Trouble speaking (stammering, lisping, hard to understand)
- (i) Missing fingers, hand, arm, toes, foot or leg
- (j) Any permanent stiffness or deformity of foot, leg, fingers, arm or back
- (k) Condition present since birth, such as club foot or cleft palate
- (l) Paralysis of any kind
- (m) Mental impairment or retardation
- (n) Arthritis
- (o) Bronchitis
- (p) Epilepsy, convulsions
- (q) Cerebral palsy
- (r) Diabetes
- (s) Anything else

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Fergusson, D.M., Horwood, L.J. "Parental Smoking and Respiratory Illness During Early Childhood: A Six-year Longitudinal Study" Pediatr Pulmonol 1(2): 99-106, 1985.

SUMMARY: The relationship between parental smoking habits and lower respiratory illness and symptoms during the first 6 years of life was studied in a birth cohort of New Zealand children. This showed that maternal (but not paternal) smoking was associated with significant increase in rates of lower respiratory infection and lower respiratory symptoms during the child's first 2 years. This association persisted when a range of perinatal, social and familial factors were taken into account statistically. After two years there was no detectable association between parental smoking habits and lower respiratory infection. Further, there was no evidence to suggest that children whose parents smoked had increased risks of asthma or rates of asthmatic attacks during early childhood.

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Parental Smoking and Respiratory Illness During Early Childhood: A Six-year Longitudinal Study

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Summary. The relationship between parental smoking habits and lower respiratory illness and symptoms during the first 6 years of life was studied in a birth cohort of New Zealand children. This showed that maternal (but not paternal) smoking was associated with significant increase in rates of lower respiratory infection and lower respiratory symptoms during the child's first 2 years. This association persisted when a range of perinatal, social and familial factors were taken into account statistically. After two years there was no detectable association between parental smoking habits and lower respiratory infection. Further, there was no evidence to suggest that children whose parents smoked had increased risks of asthma or rates of asthmatic attacks during early childhood. (Key words: asthma; children; cigarette smoking; lower respiratory illness; parental smoking.) *Pediatr Pulmonol* 1985; 1:99-106

A number of studies have examined the relationship between parental smoking and lower respiratory illness in children¹⁻¹² and, in general, the results have suggested that parental smoking may be harmful to children. Perhaps the best-documented findings relate to the increased rates of lower respiratory infection and symptoms that have been observed in children under 2 years of age whose parents (and, particularly, the mothers) smoke.¹⁻¹² This association has been found in a variety of studies that have used both retrospective and concurrent measures of medical consultation for lower respiratory infection,¹⁻¹² maternal reports of lower respiratory symptoms,¹⁻¹² and hospital attendance data.¹⁻¹² The correlation has been shown to persist when a large number of potentially confounding factors have been controlled, including family social background,¹⁻¹² family composition,¹⁻¹² lower respiratory illness in the child's family,¹⁻¹² infant feeding practices,¹⁻¹² and perinatal history.¹⁻¹² In at least two studies the association in children between early lower respiratory illness and parental smoking has been shown to disappear at around 2 years of age.¹⁻¹²

A further series of studies have suggested that, in school-aged children, parental smoking and, particularly, maternal smoking is associated with increased rates of lower respiratory

symptoms,¹⁻¹² lower respiratory infection,¹⁻¹² and reduced pulmonary function.¹⁻¹² The introduction of control factors, including measures of family social background¹⁻¹² and the children's smoking habits,¹⁻¹² has not appreciably altered these correlations. At the same time, not all studies of school-aged populations have found linkages between parental smoking and pulmonary function.¹⁻¹²

A number of investigators have also examined the relationship between parental smoking and the onset and frequency of asthma during childhood, and the majority of studies¹³⁻¹⁷ have failed to find any tendency for the children of parents who smoke to be more prone to asthma than those of nonsmokers. An exception to this trend, however, was reported by Gortmaker et al.,¹⁸ who found a small but statistically significant tendency for children whose parents smoked to suffer greater rates of asthma.

Although the general conclusion that may be drawn from this literature is that smoking is harmful for children, some aspects of the findings suggest that this relationship may not be a simple one. In particular, the emerging evidence tends to suggest that the effects of parental smoking vary with the age of the child (being most marked during early childhood), the source of the parental smoke (with maternal smoking having a greater influence than paternal smoking), and the disease that is studied (with lower respiratory infection and symptoms being more influenced by parental smoking habits than childhood asthma).

To place these issues in perspective, this pa-

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per reports the results of a six-year longitudinal study of the relationship between parental smoking habits and lower respiratory illness in children in a sample of New Zealand children. The aims of the paper are: 1) To examine the relationship between rates of lower respiratory infection or symptoms in children, parental smoking habits, and the children's ages and to devise a statistical model describing the linkages between these variables. 2) To examine the association between parental smoking and the onset of asthma and the frequency of asthmatic attacks during early childhood.

Method

The data were collected during the first eight stages of the Christchurch Child Development Study. A birth cohort of children born in the Christchurch (New Zealand) urban region in mid-1977 was studied at birth, 4 months, and annual intervals to the age of 6 years using a combination of a home-based interview with the mother supplemented by information from hospital records, general practitioner notes, and other documentary sources. The general methods of data collection and the quality control of the data have been described in previous papers.¹⁻³ The following information was used in the present analysis.

Medical Consultation for Lower Respiratory Infection. Information on medical consultations for bronchitis, bronchiolitis, and pneumonia was collected for each child for each year of life. This information was gathered from several sources including maternal recall, diaries of the children's health that were kept each year by the mothers, and information from general practitioner records.

Maternal Reports of Lower Respiratory Symptoms. Mothers were questioned about whether their child had had a "chesty cold" or "wheezy chest" at each year of life irrespective of whether a medical consultation had been involved. Separate items for chesty cold and wheeze were used for children up to 2 years of age. However, during the first year of the study, our interviewers reported that many mothers had difficulty distinguishing between wheeze and general chestiness. To overcome this possible ambiguity, from the second year onward we used a single item that covered both chesty cold and wheeze. The measure used in this analysis is based on whether at each year of life, the mother reported that her child had suffered from

chesty colds or wheeze irrespective of whether medical attention was sought for these conditions.

Asthma During Early Childhood. To measure whether a child was prone to asthma and, if so, the frequency of the asthmatic attacks, four measures were developed:

1.—whether the child had ever attended a medical practitioner for the treatment of wheeze that had been diagnosed as asthma or wheezy bronchitis. (Wheezy bronchitis was included in the definition of asthma on the basis of Williams and McNicol's⁴ conclusion that the two conditions are indistinguishable; however, only 8% of all diagnoses were for wheezy bronchitis.)

2.—whether the mother had ever reported that her child had suffered an asthmatic attack irrespective of whether this attack had been treated medically.

3.—the frequency of medical attendance from birth to 6 years for episodes of wheeze that were diagnosed as asthma or wheezy bronchitis.

4.—the frequency of maternal reports of asthmatic episodes during the period from birth to 6 years irrespective of whether medical attendance was sought.

The first two measures defined the proportion of children who, according to medical diagnosis or maternal belief, were prone to asthma; the second two measures described the frequency of asthmatic attack among those children who were susceptible to asthma.

Parental Smoking. At each year, mothers were questioned about their daily cigarette intake and the intake of the child's father.

Control Factors

To take account of the possibility that any apparent correlations between parental smoking and lower respiratory illness could have arisen from the effects of common confounding variables, the following measures were used for the purpose of statistical control.

Perinatal Status. Measures of the children's birthweights and estimated gestational ages were obtained from hospital records.

Family Composition and Social Background. As part of the routine data collected during the course of the study, information was available on maternal ages, family sizes, maternal educational levels, the children's ethnicity, and family socioeconomic statuses as measured by the Elley and Irving⁵ scale of socioeconomic status for New Zealand.

Family Atopy. At the initial interviews with

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Table 1—Rates per 100 Children of Medical Consultations for Bronchitis/Pneumonia and Maternal Reports of Lower Respiratory Symptoms by Age of Child and Parental Smoking Habits (Number of Children in Sample in Parentheses)

	Medical Consultation for Bronchitis/Pneumonia				Maternal Reports of Lower Respiratory Symptoms			
	0	1-10	11+	Total	0	1-10	11+	Total
Children 0-2 years								
Paternal smoking (cigs/day)								
0	14.6 (575)	22.7 (75)	25.2 (115)	17.0 (765)	60.9 (575)	66.7 (75)	70.4 (115)	62.9 (765)
1-10	9.1 (66)	14.0 (43)	23.5 (17)	12.7 (126)	54.6 (66)	74.4 (43)	70.6 (17)	63.5 (126)
11+	8.3 (120)	25.0 (52)	28.4 (81)	22.9 (253)	67.5 (120)	63.5 (52)	71.6 (81)	70.2 (253)
Total	14.7 (761)	21.2 (170)	26.3 (213)	17.8 (1144)	61.4 (761)	67.7 (170)	70.9 (213)	64.1 (1144)
Children 2-4 years								
Paternal smoking (cigs/day)								
0	13.7 (590)	9.9 (71)	17.0 (112)	13.8 (773)	53.2 (590)	59.9 (71)	58.9 (112)	54.6 (773)
1-10	16.0 (75)	8.7 (23)	20.8 (24)	15.6 (122)	60.0 (75)	34.8 (23)	58.3 (24)	54.0 (122)
11+	15.2 (105)	13.9 (36)	15.6 (64)	15.1 (205)	59.4 (105)	59.8 (36)	62.5 (64)	55.6 (205)
Total	14.9 (770)	10.8 (130)	17.0 (200)	14.3 (1100)	53.8 (770)	53.1 (130)	60.0 (200)	54.8 (1100)
Children 4-6 years								
Paternal smoking (cigs/day)								
0	11.1 (586)	17.5 (59)	10.7 (121)	11.5 (766)	51.5 (586)	55.9 (59)	53.7 (121)	52.9 (766)
1-10	6.1 (66)	17.4 (22)	13.0 (23)	9.8 (112)	51.5 (66)	60.9 (23)	70.0 (23)	57.1 (112)
11+	12.3 (106)	12.5 (41)	7.8 (77)	10.8 (223)	52.8 (106)	52.5 (40)	54.6 (77)	53.4 (223)
Total	10.8 (758)	15.4 (122)	10.0 (221)	11.2 (1101)	51.7 (758)	55.7 (122)	55.7 (221)	53.0 (1101)

the children's mothers. Information was collected on the presence (both past and present) of asthma, allergic rhinitis, and eczema in the mother, biological father, and siblings.

Breastfeeding History. From information collected from hospital notes and maternal interviews, estimates of the duration of time (if at all) the child was breastfed were obtained.

Pets in the Home. At each year, mothers were questioned about the presence of pet cats or dogs in the children's families, and an estimate of the extent of exposure to these animals was created for each child by summing the number of years the pets had been in the child's family.

Family Life Events. From two years onward, mothers were questioned about the occurrence of adverse or stressful life events using a 26-item check list based on an abbreviated version of the Holmes and Rahe¹¹ social readjustment rating scale. For each year, an estimate of the extent of exposure to stressful life events was created by summing the number of such events reported.

Sample Sizes

The initial cohort comprised 1,265 children, but as a result of emigration from New Zealand and losses to follow up, this cohort was reduced in 6 years to 1,115 children. This reduced sample represented 88% of the original cohort and 95% of those cohort members still alive and resident in New Zealand. However, throughout the analysis, sample sizes varied with the age of the children because complete data on parental smoking and respiratory illness for the full six-year period were not available for every child. (These were children who had left New Zealand, and who re-entered the study on their return.) The variations in sample size are reflected in tables 1, 4, and 5.

Results

Medical Consultation for Lower Respiratory Infection and Maternal Reports of Lower Respiratory Symptoms. Table 1 shows the associations between parental smoking habits and rates

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Table 2—Risks per 100 Children Aged 0-2 years of Bronchitis/Pneumonia and Lower Respiratory Symptoms by Maternal Smoking Adjusted for Family Size, Perinatal Status, Breastfeeding, and Family Social Circumstances

Maternal Daily Cigarette Intake	Bronchitis/Pneumonia	Lower Respiratory Symptoms
Nonsmoker	15.3	61.6
1-10 per day	19.5	65.0
11+ per day	24.5	68.2

of medical consultation for bronchitis and pneumonia and maternal reports of lower respiratory symptoms in their child during the period from birth to 6 years. (The data are presented in two-year blocks for simplicity, but a parallel analysis of the year-by-year trends in the data produced similar results.) Inspection of the table suggests that parental smoking and, particularly, maternal smoking was associated with increased rates of medical consultation and increased maternal reports of lower respiratory symptoms in the children we studied during the first two years of life. However, after the children reached 2 years of age, there appeared to be little or no association between parental smoking habits and the rates of lower respiratory illness or symptoms. These conclusions were confirmed by fitting a series of hierarchical log linear models²² to the data on rates of lower respiratory illness shown in the table. This procedure led to the following conclusions. 1) During the children's first 2 years of life, maternal smoking was associated with significant increases in rates of medical consultation for lower respiratory infection (log likelihood ratio $\chi^2 = 15.90$, df = 2, $P < 0.001$) and maternal reports of lower respiratory symptoms (log likelihood ratio $\chi^2 = 8.27$, df = 2, $P < 0.05$). Paternal smoking did not make a contribution to the variability in rates of illness when considered alone or in combination with maternal smoking. 2) After the children reached 2 years of age, there were no significant associations between parental smoking habits and rates of lower respiratory illness or symptoms.

The results in table 1 do not take into account the possible effects of other social or familiar factors that may be correlated with maternal smoking habits and childhood lower respiratory illness or symptoms. To examine this issue, the data for the first 2 years were reanalyzed using logistic regression methods²³ in which maternal smoking together with the measures of family social background, family composition, infant feeding practices, and perinatal history were related to rates of medical consultation for bronchitis and pneumonia and rates of maternal

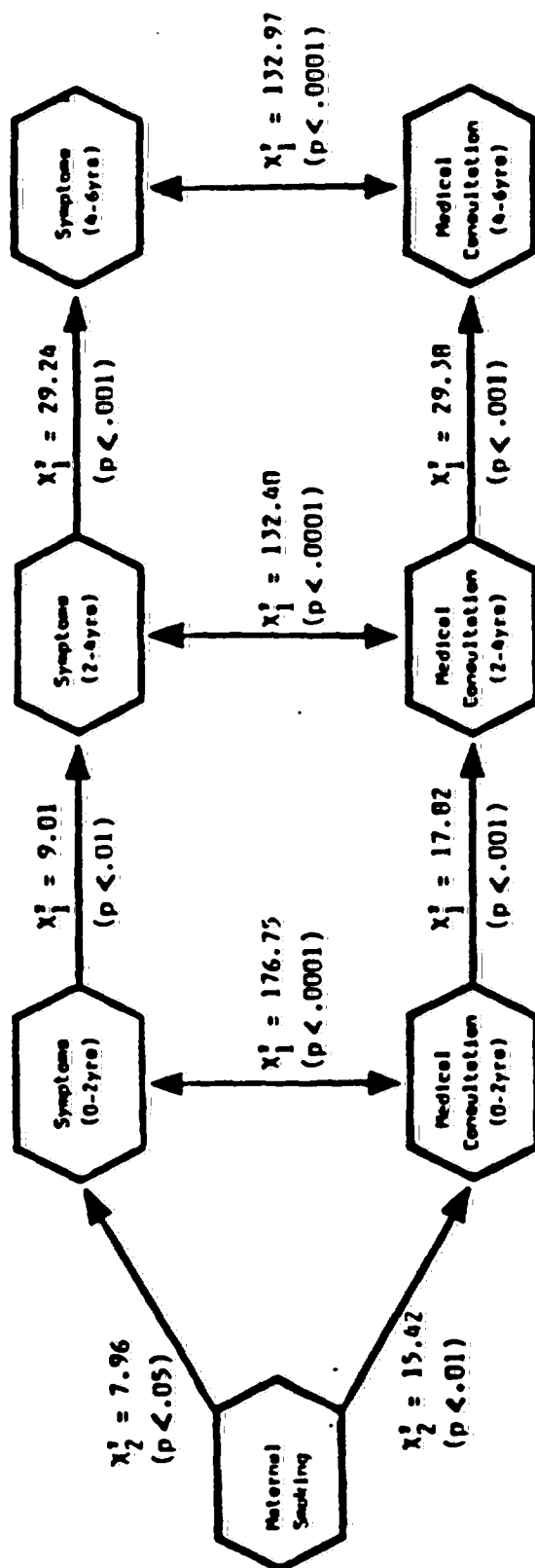
reports of symptoms. Results of this analysis clearly showed that, even when all control factors were taken into account, there was a significant association during the children's first two years between maternal smoking habits and rates of lower respiratory infection ($P < 0.01$) and a marginally significant ($P = 0.06$) association between maternal smoking habits and rates of lower respiratory symptoms. From the fitted model, estimates were obtained using the methods described by Lee²⁴ of the association between maternal smoking and rates of lower respiratory infection and symptoms that were adjusted for the effects of the control factors. The adjusted rates are shown in table 2 and indicate that the introduction of the control factors had a negligible effect on the general dose/response relationship between maternal smoking habits and rates of lower respiratory infection and symptoms in children under the age of 2 years.

Our initial analyses examined the data in a series of cross-sectional two-year blocks. To analyze the dynamic relationships that existed between maternal smoking and rates of lower respiratory illness and symptoms throughout the child's first 6 years, the data was used to form a 3×2 contingency table,²⁵ which described the associations between maternal smoking during the child's first 2 years and rates of lower respiratory infections and symptoms throughout the child's first 6 years. This table was fitted using log linear modeling methods. A summary of the analysis is shown in table 3, which gives values

Table 3—Fitted Log Linear Model of Maternal Smoking, Medical Consultations for Lower Respiratory Illness, and Maternal Reports of Lower Respiratory Symptoms, 0-6 yrs.

Factor	λ	σ^2	P
First order effects			
Maternal smoking: A			
Medical consultations 0-2 yrs: B			
Symptoms 0-2 yrs: C			
Medical consultations 2-4 yrs: D	682.68	0.1	$P < 0.0001$
Symptoms 2-4 yrs: E			
Medical consultations 4-6 yrs: F			
Symptoms 4-6 yrs: G			
Second order effects			
AB	15.42	0.1	$P < 0.01$
AC	7.96	0.1	$P < 0.05$
BC	176.75	1	$P < 0.0001$
BD	17.82	1	$P < 0.001$
CE	0.01	1	$P < 0.01$
DE	132.40	1	$P < 0.0001$
DF	96.28	1	$P < 0.0001$
EG	96.24	1	$P < 0.0001$
FG	132.57	1	$P < 0.0001$
Residual	131.75	177	$P > 0.99$

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of the log likelihood ratio chi-square statistics for the various effects in the fitted model. The results can be readily interpreted from figure 1, which shows the fitted model using the conventions described by Freeman and Jekel.¹² In this diagram, variables that were significantly related are shown linked by solid lines, and the size of the association is indicated by the log likelihood ratio chi-square value and its corresponding level of significance. Variables that were not significantly related are not linked by lines. The following conclusions can be drawn from the figure. 1) Maternal smoking was associated with significant increases in rates of lower respiratory illness ($P < 0.01$) and symptoms ($P < 0.05$) during the children's first 2 years. 2) Within each measuring period there were very strong associations ($P < 0.0001$) between medical consultations for lower respiratory illness and maternal reports of lower respiratory symptoms. These associations arose because if the child had attended a medical practitioner for lower respiratory illness, his or her mother almost invariably reported lower respiratory symptoms. 3) There were significant associations ($P < 0.001$) between rates of medical consultation for lower respiratory illness across measurement periods. Thus, lower respiratory infection during the first 2 years was significantly associated with lower respiratory infection during the period from 2 to 4 years, which in turn was associated with lower respiratory infection during the period from 4 to 6 years. A similar causal-chain model links the measures of maternal reports of lower respiratory symptoms.

As may be seen from Table 3, the model depicted in figure 1 produced a very satisfactory fit to the observed data ($\chi^2 = 131.73$; $df = 172$; $P = 0.99$).

Asthma During Early Childhood. Table 4 compares the number of children having at least one asthmatic episode (defined both on the basis of medical consultation and maternal report) by the age of 6 years with parental smoking habits. Inspection of the table shows no clear tendency for the proportions of asthmatic children to vary with parental smoking habits, and this was confirmed by log linear modeling of the results, which indicated that there was no significant association between being asthmatic and parental smoking habits.

Figure 1—Fitted log linear model of maternal smoking, medical consultation for lower respiratory illness, and maternal reports of lower respiratory symptoms in children 0-6 years of age.

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Table 4—Risks Per 100 Children of Having at Least One Asthmatic Episode by the Age of 6 Years by Parental Smoking Habits (Number of Children in Sample in Parentheses)

	Medical Consultation				Maternal Report			
	0	1-10	11+	Total	0	1-10	11+	Total
Paternal smoking (cigs/day):								
0	18.6 (460)	9.0 (67)	6.8 (74)	11.4 (601)	13.5 (460)	10.5 (67)	8.1 (74)	12.5 (601)
1-10	15.1 (86)	17.2 (64)	16.9 (65)	16.3 (215)	15.1 (86)	17.2 (64)	16.9 (65)	16.3 (215)
11+	17.2 (93)	19.3 (57)	9.1 (66)	13.4 (216)	17.2 (93)	14.0 (57)	10.6 (66)	14.4 (216)
Total	13.6 (639)	19.8 (188)	10.7 (205)	13.0 (1032)	14.2 (639)	13.8 (188)	11.7 (205)	13.7 (1032)

However, the results in table 4 do not take into account the possibility that, while parental smoking may not influence the child's predisposition to asthma, it may influence the frequency of asthmatic attacks among those susceptible to asthma. This issue is examined in table 5, which shows the frequency of asthmatic attacks per 100 children (measured both on the basis of maternal report and frequency of medical consultation) related to parental smoking habits. While there was substantial variability in the rates of asthmatic attacks depending on the combinations of parental smoking, there was no clear trend in the results that would suggest increased parental smoking was associated with increases in the rate of asthmatic attacks. This impression was confirmed by log linear modeling of the data in table 5, which showed there were no significant associations between parental smoking and the frequency of asthmatic attacks.

To examine the possible effects of various confounding factors on the associations between parental smoking and the occurrence of asthma in children and the rates of asthmatic attacks, the data were further analyzed using regression methods in which a number of control factors, including gender, family history of asthma, early eczema, early respiratory infection, breastfeeding history, pets in the family, family life events, and family social background were introduced as factors in stepwise analyses. The analysis of the risk data in table 4 was conducted using multiple logistic regression, whereas the frequency of attack data (table 5) were analyzed using multiple linear regression methods based on the square root of the number of episodes of asthma occurring during the period from 0-6 years. All analyses indicated that there were no significant relationships between parental smoking habits and risks of childhood asthma or rates of asthmatic attacks even when the set of control factors was taken into account statistically.

Discussion

The findings of this six-year longitudinal study indicate that the effects of parental smoking on childhood respiratory illness depended on the child's age, the source of parental smoke, and the outcome studied. There was clear evidence of a relationship during the child's first 2 years between maternal (but not paternal) smoking and both an increased rate of medical consultations for bronchitis/pneumonia and increased reports of lower respiratory symptoms. However, after this time, maternal smoking did not make a significant contribution to the rates of medical consultation or reports of lower respiratory symptoms. Paternal smoking was not related to lower respiratory illness at any time, and neither paternal nor maternal smoking was related to the risk of asthma or the frequency of asthmatic attacks during the child's first 6 years.

The finding of an association between lower respiratory illness or symptoms and parental smoking during the first two years of life confirms the findings of a number of previous studies^{1,2,10,11} and, as remarked earlier, the correlation appears to be resilient to the effects of statistical and other controls. Collectively, the available evidence strongly suggests that maternal smoking increases rates of lower respiratory illness and symptoms in children up to the age of 2 years. However, the mechanisms involved are as yet unclear. Colley et al.⁹ proposed a genetic explanation in which parental smoking is related to a genetic disposition to lower respiratory illness, which is reflected in higher rates of morbidity among the offspring of smokers. However, this explanation seems highly unlikely given that, according to most studies, maternal smoking is more important in this regard than is paternal smoking, which would suggest a mode of inheritance in which a predisposition to lower respiratory illness is sex linked to the child's mother.⁹ Fergusson et al.⁸ have suggested

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Table 5—Rate Per 100 Children Aged 0-6 Years of Asthmatic Attacks by Parental Smoking (Number of Children in Sample in Parentheses)

	Medical Consultation				Maternal Report			
	Parental Smoking (cigs/day)				Parental Smoking (cigs/day)			
	0	1-10	11+	Total	0	1-10	11+	Total
Paternal smoking (cigs/day)								
0	57.4 (460)	49.3 (67)	56.8 (74)	56.4 (601)	124.6 (460)	79.1 (67)	101.4 (74)	116.6 (601)
1-10	76.7 (86)	34.4 (64)	79.3 (65)	62.8 (215)	166.3 (86)	98.4 (64)	90.5 (65)	156.7 (215)
11+	95.7 (93)	38.6 (57)	56.1 (66)	68.5 (216)	163.4 (93)	59.7 (57)	130.2 (66)	125.9 (216)
Total	65.6 (639)	41.0 (188)	61.5 (205)	60.3 (1032)	135.8 (639)	79.8 (188)	142.4 (205)	126.9 (1032)

a hypothesis in which prolonged exposure to cigarette smoke has an irritant effect that exacerbates the respiratory infections that normally occur during early childhood, making it more likely that lower respiratory symptoms will develop.

However, whereas previous studies¹¹⁻¹⁴ have reported associations between lower respiratory symptoms, lower respiratory illness or impaired pulmonary function, and parental smoking for school-aged children, we were unable to find any association between parental smoking and respiratory illness or symptoms during the period from 2-6 years. It seems possible that this may reflect the age of the children studied. In particular, it seems likely that prolonged exposure to parental smoke may have an accumulative effect¹⁵ on pulmonary function and susceptibility to lower respiratory illness, and it is possible that our sample of children was too young for any increase in rates of morbidity or symptoms to be detected. In contrast, the previous studies that have demonstrated associations in school-aged children have examined older populations or populations with a wider age range than our sample.

It has been suggested that the association between parental smoking and lower respiratory symptoms and illness in school-aged children may reflect the indirect consequences of early exposure to cigarette smoke. Tager et al.¹⁶ argue that such early exposure coupled with increased risks of early lower respiratory illness may cause structural changes that are reflected in increased rates of lower respiratory symptoms and reduced pulmonary function during later childhood. The results of the longitudinal log-linear analysis presented in this paper cast some light on the plausibility of this hypothesis. In particular, the model suggested that maternal smoking was associated with an increased risk of lower respiratory illness and symptoms during the child's first 2 years, and that early respira-

tory illness or symptoms during the first 2 years are associated with subsequent illness or symptoms. At first sight these results would appear to support the hypothesis that early exposure to parental smoke leads to later respiratory illness. However, this view does not take into account the statistical "slippage" that occurs within this system of relationships. Thus, while maternal smoking does influence early respiratory illness, and early respiratory illness is related to later respiratory illness, maternal smoking made a negligible direct or indirect contribution to later respiratory illness for our cohort. This suggests that the tendency for rates of lower respiratory illness or symptoms to be correlated over time cannot be attributed to the common effects of maternal smoking on respiratory function.

A more plausible explanation of the existing data would appear to be that there are two mechanisms involved in the correlations between parental smoking and lower respiratory illness and symptoms in children. First, during early childhood there is a short-term effect by which exposure to cigarette smoke has the effect of increasing the likelihood of early respiratory illness. This effect is relatively short lived and disappears at around the age of 2 years. However, in the light of the findings of Tager et al.¹⁶ there is also evidence to suggest that prolonged exposure to parental smoking may have the effect of gradually compromising the lower respiratory system of children so that around the middle-school years, children become at greater risk of lower respiratory illness and reduced pulmonary function.

In confirmation of three previous studies,¹¹⁻¹³ we were unable to show any correlation between parental smoking and either the onset or frequency of asthmatic attacks during early childhood. These results suggest that, while parental smoking may predispose children to develop lower respiratory illness and symptoms, it is not implicated in the development of asthma or the

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frequency of asthmatic attacks in young children. At the same time, Gortmaker et al.²² were able to show a small but nonetheless significant association between parental smoking habits and asthma in a cross-sectional sample of children aged from 0–17 years. It seems possible that these differences may reflect age differences between samples. If, as was conjectured previously, prolonged exposure to cigarette smoke has a subtle, long-term effect on respiratory function, it is possible that an association between parental smoking and childhood asthma exists only in older children who have experienced sufficient exposure to parental smoke to increase their susceptibility to asthmatic attacks. It should also be noted that the apparent correlation between parental smoking and asthma reported by Gortmaker et al.²² could be a disguised correlation between asthma and smoking in the child,^{20,21} as this factor was not controlled for in their analyses.

Finally, while the results of this study support the general conclusion that parental smoking may be harmful to children, the results suggest the possibility of complex relationships between the child's age, duration of exposure to smoke, and various measures of respiratory illness and function. Such relationships can only be clarified by further longitudinal studies that examine the way in which varying exposure times to parental smoking have dynamic effects on both the susceptibility to lower respiratory illness and pulmonary function throughout childhood.

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ABSTRACT. The role of social and familial factors in the development of childhood asthma by age 6 years was studied in a birth cohort of New Zealand children. Rates of asthma varied markedly with the child's sex; boys had twice the rate of asthma as girls. In addition, the factors associated with asthma varied with the child's sex. For boys, wheeze during infancy, early eczema, and parental asthma were all significant risk factors; for girls, the only risk factor was early eczema. Proportional hazards modeling of the data failed to show any significant associations between the development of asthma and a large range of other social and familial factors including breast-feeding, parental smoking habits, pets in the child's family, stress in the family, or family social background. It was concluded that asthma in early childhood appeared to be inherited to some extent, its age of expression was related to the child's sex, and it had a complex interaction with other forms of allergic disease. There was no evidence to suggest that the structure, practices, or dynamics of the child's family played a significant role in the development of asthma for children in this birth cohort.

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Social and Familial Factors in the Development of Early Childhood Asthma

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ABSTRACT. The role of social and familial factors in the development of childhood asthma by age 6 years was studied in a birth cohort of New Zealand children. Rates of asthma varied markedly with the child's sex; boys had twice the rate of asthma as girls. In addition, the factors associated with asthma varied with the child's sex. For boys, wheeze during infancy, early eczema, and parental asthma were all significant risk factors; for girls, the only risk factor was early eczema. Proportional hazards modeling of the data failed to show any significant associations between the development of asthma and a large range of other social and familial factors including breast-feeding, parental smoking habits, pets in the child's family, stress in the family, or family social background. It was concluded that asthma in early childhood appeared to be inherited to some extent, its age of expression was related to the child's sex, and it had a complex interaction with other forms of allergic disease. There was no evidence to suggest that the structure, practices, or dynamics of the child's family played a significant role in the development of asthma for children in this birth cohort. *Pediatrics* 1985;75:859-868; *childhood asthma, breast-feeding, smoking, parental asthma.*

There have been a large number of studies of the social and familial factors associated with childhood asthma. Among the factors that have been suggested to lead to increased risks of asthma are: a family history of asthma¹⁻¹⁰ and other atopic conditions^{5,10}; a history of other atopic conditions in the child^{6,7,11,12}; viral respiratory infections in early childhood¹³⁻¹⁶; the child's sex^{4,12,13,17}; psychosocial and family stress factors¹⁸⁻²¹; artificial

feeding^{9,22-24}; parental smoking^{25,26}; the presence of cats and dogs in the home^{9,27}; and social background.^{12,26,28-31}

However, the conclusions drawn from these studies have been limited by the fact that they have often been conducted upon small samples, from selected clinical populations, using cross-sectional or retrospective case-control designs. There appears to have been no prospective study that has examined the role of social and familial factors in the development of asthma in a large and representative population of children.

This paper reports on the results of a 6-year prospective study of the development of asthma in a birth cohort of New Zealand children. The aims of the study were: (1) to identify the social and familial factors associated with increased risks of asthma in early childhood, and (2) to develop a proportional hazards model to describe the way in which various social and familial factors and combinations of these factors influenced the likelihood of developing asthma.

METHOD

The data were collected during the first 6 years of the Christchurch Child Development Study. In this study, a birth cohort of Christchurch (New Zealand) children has been studied at birth, age 4 months, and at annual intervals to age 6 years. At each stage, information was collected on the child's health, family social background, and other factors by means of a structured interview with the child's mother supplemented by information from hospital records, general practitioner's notes, and diary of medical attendances kept by the mother. The methods of data collection and quality control have been described in detail in previous papers.^{7,32-36}

From the data base of the study the following

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variables were selected for analysis: childhood asthma, family history of atopy, child health in the first year, early feeding and home environment, psychosocial factors, and family social background.

Childhood Asthma

This was based on whether the child had made two medical consultations before the age of 6 years for wheeze or associated symptoms that were diagnosed as asthma or wheezy bronchitis. Wheezy bronchitis was included in the definition of asthma on the basis of the conclusions of Williams and McNicol³⁶ that the two conditions were indistinguishable. (Only 8% of all diagnoses were for wheezy bronchitis.) The criterion of at least two diagnoses was used as there is some uncertainty about the significance of a single diagnosis of asthma in early childhood. The frequency distribution of the number of medical attendances for asthma is given in Table 1, which shows that by age 6 years, 10.3% of cohort members had made two or more attendances. In all cases, the diagnosis of asthma or wheezy bronchitis was made after the child was 1 year old. An analysis of the effects of varying the stringency of the definition of asthma and of excluding diagnoses of wheezy bronchitis is given under "Results." Information on childhood asthma and wheezy bronchitis was obtained from an annual diary of medical attendances kept by the child's mother in 60% of cases. In the remaining 40% of cases, this information was based on maternal recall supplemented by direct contacts with the child's family doctor.^{7,35} The majority (94%) of asthmatic attacks were treated by the child's family doctor, but nonetheless 24 of the 109 (22%) children who suffered two or more asthmatic episodes had been admitted to hospital for asthma.

Family History of Atopy

Information on the history of atopic conditions (both past and present) in both of the child's biologic parents and among the child's full siblings

TABLE 1. Frequency Distribution of Number of Medical Consultations for Asthma (Ages 0 to 6 Years)

No. of Consultations	No.	%
0	915	86.6
1	32	3.0
2	26	2.5
3	20	1.9
4	12	1.1
5-9	25	2.4
10-14	13	1.2
15+	13	1.2
Total	1,056	100.0

was collected prospectively at the initial (birth) interview.⁷ From this information, four dichotomous measures were constructed: (1) parental asthma—whether there was a known history of asthma in one or both parents; (2) parental eczema—whether there was a known history of eczema in one or both parents; (3) parental allergic rhinitis—whether there was a known history of allergic rhinitis in one or both parents; and (4) sibling asthma—whether there was a known history of asthma in any of the child's full siblings. For the measures of parental atopy, consideration was given to analyzing both maternal and paternal atopy separately. However, it was found that combined indices based on a history of atopy in either parent were as effective predictors as measures based on data for each parent.

Child Health in First Year

The following measures were constructed on the basis of maternal reports, diary records, and records of general practitioner and hospital attendances in the first year: (1) eczema—whether the child had at least one medical attendance for skin rash that was diagnosed as eczema^{33,34} (Because information on medical attendances for eczema were based on maternal reports supplemented by information from medical records, it was not possible to distinguish reliably between atopic and seborrheic eczema.); (2) wheeze—whether the child had attended a medical practitioner for wheezy chest not diagnosed as asthma, or the mother reported respiratory wheeze that did not require medical attention^{37,38}; (3) lower respiratory tract infections—the total number of episodes of bronchitis, bronchiolitis, or pneumonia treated by a medical practitioner^{37,38}; and (4) total respiratory infections—the total number of episodes of respiratory tract illness (either upper or lower) treated by a medical practitioner.³⁷

Early Feeding and Home Environment

The following measures were used as indicators of the child's early feeding history and home environment:

Infant Milk Diet (Age 0 to 4 Months). This was based on information collected from (1) obstetric unit notes of the child's feeding history shortly after birth, (2) a diary record kept by the mother on the child's feeding history from birth to age 4 months (85% of mothers kept such a diary), and (3) questioning the mother about the child's feeding history to determine whether he or she had ever been given any cow's milk. (A detailed account of methods for assessing the breast-feeding history of this cohort has been published previously.³³⁻³⁵)

The early milk feeding history of the sample was classified as follows: (1) children who had been totally bottle fed since birth and never received any breast milk; (2) children who had been breast-fed but who had received some cow's milk before age 4 months; and (3) children whose early milk diet was breast milk only and who had never received cow's milk by age 4 months.

Parental Smoking. Each year, information was collected on the smoking habits of the child's parents. The history of parental smoking over the survey period was classified as follows: (1) neither parent smoked at any time; (2) one parent smoked at some time during the survey period; and (3) both parents smoked at some time during the study period.

Cats/Dogs in the Home. Records included information on whether the family had a pet cat or dog.

Psychosocial Factors

To measure the amount of stress, adversity, and social readjustment experienced by the family during the study period the following three measures were constructed.

Family Life Events to Age 6 Years. Each year from 2 years to 6 years, mothers were interviewed using a modified version of the Holmes and Rahe Social Readjustment Rating Scale.³⁹ This consisted of 20 items which covered such areas as illness in the family, bereavement, financial problems, and marital disharmony. The characteristics of the scale have been described in detail by Beautrais et al.³² To measure the amount of adversity faced by the family, a life events score was constructed by summing the total number of life events reported over the study period.

Maternal Depression. At 5 years and 6 years, mothers were interviewed on a modified version of the Levine-Pilowsky Depression Questionnaire.^{40,41} The scale consisted of 37 items measuring various symptoms of depression. The characteristics of the scale have been described by Fergusson et al.⁴² To measure the mother's general level of depression, a scale score was constructed by summing the total number of depressive symptoms reported by the mother over the 2-year period.

Changes of Residence. Records included information on the number of changes of residence experienced by the child from birth to age 6 years.

Family Social Background

The following measures were used as indicators of the family's social situation: (1) maternal age at the birth of the survey child; (2) maternal education classified as—no formal qualifications, secondary

qualifications (NZ School Certificate or University Entrance), or tertiary qualifications (University degree or tertiary technical diploma); (3) child's ethnic status—Maori/Pacific Island v European/other; (4) family socioeconomic status—based on the Elley-Irving⁴³ scale of socioeconomic status for New Zealand, which classifies the population into six classes on the basis of parental occupation; and (5) family size at the child's birth.

Sample Size and Response Rates

The analysis is based on a total of 1,056 children for whom complete data on all the variables in the analysis were available. This number represents 83% of the initial cohort of 1,265 children and 91% of the cohort of children who were still alive and resident in New Zealand at age 6 years. Comparison of the obtained sample with the characteristics of the initial cohort indicated that no significant biases had been introduced as a result of sample attrition.

RESULTS

Risk Factors Associated with Development of Asthma

The association between the proportions of children experiencing two or more episodes of asthma by age 6 years and a series of measures of family and social background is shown in Table 2. The results are shown separately for boys and girls, and each association is tested for statistical significance by the χ^2 test. As shown in Table 2: (1) The rate of asthma was higher among boys than girls: 14.3% of boys had developed asthma by age 6 years in contrast to only 6.3% of girls ($\chi^2 = 18.20$; $df = 1$; $P < .0001$). (2) The factors associated with increased risks of asthma differed markedly between the sexes. For girls, the only significant risk factor was eczema in the first year: girls who had eczema were five times more likely to develop asthma ($P < .0001$). For boys, there was also a significant association between asthma and early eczema ($P < .0001$). However, in contrast to girls, boys were more likely to develop asthma when there was a history of early wheeze ($P < .0001$); when there was a parental history of asthma ($P < .0001$) or allergic rhinitis ($P < .01$); and when other siblings had asthma ($P < .01$). (3) For both sexes there were no apparent associations between rates of asthma and breast-feeding, parental smoking, the presence of cats and dogs, various stresses in the family and family social background.

Because many of the variables in Table 2 were intercorrelated, the results do not indicate the net

TABLE 2. Proportions of Children with Two or More Medical Consultations for Asthma (Ages 0 to 6 Years) by Sex of Child and Familial and Social Factors

Variable	Boys	Girls	Total
Family history of atopy			
Parental asthma			
No asthma	11.2 (48/428)	5.8 (25/433)	8.5 (73/861)
Asthma	26.9 (28/104)	8.8 (8/91)	18.5 (36/195)
Significance	$P < .0001$	NS	$P < .0001$
Parental eczema			
No eczema	12.8 (54/422)	5.8 (23/397)	9.4 (77/819)
Eczema	20.0 (22/110)	7.9 (10/127)	13.5 (32/237)
Significance	NS	NS	NS
Parental allergic rhinitis			
No allergic rhinitis	11.2 (39/347)	5.8 (21/363)	8.5 (60/710)
Allergic rhinitis	20.0 (37/185)	7.5 (12/161)	14.2 (49/346)
Significance	$P < .01$	NS	$P < .01$
Sibling asthma			
No siblings with asthma	12.8 (60/469)	6.2 (30/483)	9.5 (90/952)
Siblings with asthma	25.4 (16/63)	7.3 (3/41)	18.3 (19/104)
Significance	$P < .01$	NS	$P < .01$
Child health in first year			
Eczema			
No eczema	12.1 (59/489)	4.9 (24/488)	8.5 (83/977)
Eczema	39.5 (17/43)	25.0 (9/36)	32.9 (26/79)
Significance	$P < .0001$	$P < .0001$	$P < .0001$
Wheeze			
No wheeze	8.9 (26/293)	6.5 (21/325)	7.6 (47/618)
Wheeze	20.9 (50/239)	6.0 (12/199)	14.2 (62/438)
Significance	$P < .0001$	NS	$P < .001$
Lower respiratory tract infections			
0	13.5 (64/474)	6.2 (30/482)	9.8 (94/956)
At least 1	20.6 (12/58)	7.1 (3/42)	15.0 (15/100)
Significance	NS	NS	NS
Total respiratory tract infections			
0	14.6 (25/171)	7.7 (14/181)	11.1 (39/352)
1-2	11.8 (31/262)	5.2 (13/250)	8.6 (44/512)
3+	20.2 (20/99)	6.5 (6/93)	13.5 (26/192)
Significance	NS	NS	NS
Feeding and home environment factors			
Infant milk diet (0-4 mo)			
Bottle milk only	13.0 (16/123)	7.1 (8/113)	10.2 (24/236)
Breast milk and bottle milk	13.3 (42/315)	5.7 (18/314)	9.5 (60/629)
Breast milk only	19.1 (18/94)	7.2 (7/97)	13.1 (25/191)
Significance	NS	NS	NS
Parental smoking			
Neither parent smoked	14.6 (33/226)	7.4 (17/229)	11.0 (50/455)
One parent smoked	12.0 (21/175)	7.1 (12/169)	9.6 (33/344)
Both parents smoked	16.8 (22/131)	3.2 (4/126)	10.1 (26/257)
Significance	NS	NS	NS
Cats/dogs in home			
No	14.4 (15/104)	11.2 (10/89)	12.9 (25/193)
Yes	14.2 (61/428)	5.3 (23/435)	9.7 (84/863)
Significance	NS	NS	NS
Psychosocial factors			
Family life events (1-6 yr)			
0-4 events	12.7 (10/79)	4.7 (5/107)	8.1 (15/186)
5-9 events	13.5 (29/215)	6.6 (13/197)	10.2 (42/412)
10-14 events	15.5 (23/148)	4.8 (5/104)	11.1 (28/252)
15+ events	15.6 (14/90)	8.6 (10/116)	11.7 (24/206)
Significance	NS	NS	NS
Maternal depression score (5-6 yr)			
0-4 symptoms	11.4 (29/255)	5.3 (13/244)	8.4 (42/499)
5-9 symptoms	16.8 (16/95)	8.2 (9/110)	12.2 (25/205)
10-14 symptoms	22.4 (15/67)	5.3 (3/57)	14.5 (18/124)
15-19 symptoms	18.9 (7/37)	4.8 (2/42)	11.4 (9/79)
20+ symptoms	11.5 (9/78)	8.5 (6/71)	10.1 (15/149)
Significance	NS	NS	NS

TABLE 2—Continued

Variable	Boys	Girls	Total
Changes of residence (0–6 yr)			
0	12.0 (22/183)	6.0 (11/182)	9.0 (33/365)
1–2	16.4 (33/201)	5.2 (10/194)	10.9 (43/395)
3–4	15.1 (13/86)	5.6 (5/89)	10.3 (18/175)
5+	12.9 (8/62)	11.9 (7/59)	12.4 (15/121)
Significance	NS	NS	NS
Family social background			
Maternal age			
<20 yr	19.1 (9/47)	4.3 (2/47)	11.7 (11/94)
20–24 yr	14.5 (25/172)	7.4 (11/148)	11.3 (36/320)
25–29 yr	15.5 (31/200)	7.2 (16/221)	11.2 (47/421)
≥30 yr	9.7 (11/113)	3.7 (4/108)	6.8 (15/221)
Significance	NS	NS	NS
Maternal education			
No formal qualifications	15.5 (42/271)	6.2 (17/273)	10.8 (59/544)
Secondary qualifications	13.3 (22/166)	6.4 (9/140)	10.1 (31/306)
Tertiary qualifications	12.6 (12/95)	6.3 (7/111)	9.2 (19/206)
Significance	NS	NS	NS
Child's ethnic status			
Maori/Pacific Island	18.5 (15/81)	3.0 (2/66)	11.6 (17/147)
European/other	13.5 (61/451)	6.8 (31/458)	10.1 (92/909)
Significance	NS	NS	NS
Socioeconomic status			
Professional, executive	14.9 (15/101)	4.3 (5/116)	9.2 (20/217)
Clerical, technical, skilled	12.8 (36/282)	6.3 (18/284)	9.5 (54/566)
Semiskilled, unskilled, unemployed	16.8 (25/149)	8.1 (10/124)	12.8 (35/273)
Significance	NS	NS	NS
Family size			
1	11.9 (25/210)	6.8 (13/190)	9.5 (38/400)
2	15.4 (28/182)	6.7 (13/195)	10.9 (41/377)
3	15.3 (15/98)	7.1 (7/99)	11.2 (22/197)
4+	19.0 (8/42)	0.0 (0/40)	9.8 (8/82)
Significance	NS	NS	NS
Total	14.3 (76/532)	6.3 (33/524)	10.3 (109/1056)

contributions of each of the factors to the rate of asthma during the 6-year period. We describe below a proportional hazards regression model designed to estimate the net effects of the predictor variables on rates of asthma for boys and girls over the period from ages 1 to 6 years.

Proportional Hazards Model of Development of Asthma

The mathematical basis of the proportional hazards model can be summarized briefly as follows. (For a complete mathematical formulation of the model the reader is referred to Cox⁴⁴ or Kalbfleisch and Prentice.⁴⁵) Consider some population or sample observed over a series of time intervals (t) during which some subjects are observed to fail (ie, become asthmatic). The distribution of failures over time defines the survivorship function: $S_t = \Pr(T \geq t)$, where S_t denotes the survivorship probability (\Pr) to time t and T is the time to failure.

Associated with the survival function is the haz-

ard function $\lambda(t)$. The hazard at any time t is defined as the conditional probability of failure at time t , given that failure has not occurred prior to this time. An alternative and intuitively more meaningful description of the hazard is the instantaneous failure rate.

Next, consider the situation in which subjects may be classified according to some series of variables or covariates that are assumed to influence the likelihood of failure. Let these covariates be represented by a vector of values z for each subject. The aim of the proportional hazards model is to describe the way in which the hazard varies over time with the set of covariate values. The model assumes the existence of a base-line group of subjects whose vector of covariate values is arbitrarily set to zero. It is also assumed that the effects of the covariate values are to scale the hazard over time in a way that is proportional to the hazard function for this base-line group. This model is: $\lambda(t; z) = \lambda_0(t)e^{z\beta}$, where $\lambda(t; z)$ denotes the hazard at time t for a group of subjects with covariate vector z , $\lambda_0(t)$

is the hazard at time t for the base-line population with covariate values of 0, and β is a vector of regression-like coefficients. The parameters of the model may be estimated by maximum likelihood techniques, and estimates of the asymptotic standard errors of the coefficients β are available.⁴⁶

To examine the net contributions of the risk factors in Table 2 to variations in rates of asthma, a stepwise proportional hazards model was fitted to the data. In this analysis, the age at which the child first developed asthma was defined as the point at which the first of at least two medical attendances for asthma or wheezy bronchitis occurred. In view of the differences seen in Table 2, separate models were fitted for boys and girls. This analysis showed that when all variables were considered, only three of these (parental asthma, early wheeze, early eczema) were significantly related to the development of asthma in boys. For girls, the only significant risk factor was early eczema. The results of the analysis are summarized in Table 3, which shows the significance of each of the risk factors in the model and the values of the proportional hazards coefficient (e^{β}) for each level of each variable. This coefficient may be interpreted in a way that is analogous to the more familiar notion of relative risk: the increase in the instantaneous risk of asthma that is associated with a particular factor when compared with the risk for the base-line population. Definitions of the base-line populations for boys and girls are given in the footnote to Table 3. For boys, the presence of eczema increased the risk of asthma by 3.45 times over the risk for the base-line group; a parental history of asthma increased the risk by a factor of 2.78; and wheeze in the first year by a factor of 2.39. For girls, the presence of early eczema increased the risk of asthma by a factor of 5.80.

From the results of proportional hazards analysis, estimates were obtained of the risk of experi-

encing two or more episodes of asthma by the age of 6 years conditional on various combinations of risk factors. The results of this analysis are summarized in Table 4, which shows the estimated cumulative rate of asthma at each age conditional on the number of significant factors that the child had. For boys, three factors—early eczema, early wheeze, and parental asthma—were considered; for girls, the only factor was early eczema. The results show: (1) For boys there was considerable variation in the risk of asthma conditional on the number of significant risk factors that were present. Boys who had all three factors (early eczema, early wheeze, and parental asthma) had a probability of approximately 80% of developing asthma by age 6 years. In contrast, those with none of these factors had a risk of only 7%. The groups of subjects with one or two of the risk factors had results that lay between these extremes. (2) For girls, variations in prognosis were less marked. However, girls who developed early eczema had rates of asthma that were slightly more than five times higher than girls who did not have early eczema.

Sensitivity Analysis

Gregg⁴ notes that estimates of the prevalence of asthma depend on the stringency of the criteria used to define the condition. To examine the effects of varying the stringency of the definition of asthma on both the prevalence of asthma and the factors associated with the condition, the results were re-analyzed using a series of definitions of asthma of increasing stringency. These definitions required that the child was classified as asthmatic only after he or she had suffered 3, 4, 5, or 6 episodes of wheeze medically diagnosed as asthma or wheezy bronchitis. The results of this analysis are given in Table 5, which shows for each definition the estimated rate of asthma for boys and girls and the proportional hazards coefficients for each risk factor for each analysis. The table shows: (1) The estimated rate of asthma varied sharply with vary-

TABLE 3. Estimated Proportional Hazards Coefficients for Levels of Significant Factors

Variable	Boys* e^{β}	Significance	Girls* e^{β}	Significance
Child eczema				
No eczema	1		1	
Eczema	3.45	$P < .001$	5.80	$P < .001$
Child wheeze				
No wheeze	1		...	
Wheeze	2.39	$P < .001$...	NS
Parental asthma				
No asthma	1		...	
Asthma	2.78	$P < .001$...	NS

* Base-line populations for the two models are: (1) for boys—children with no eczema or wheeze in the first year and without a history of parental asthma; (2) for girls—children with no eczema in the first year.

TABLE 4. Estimated Cumulative Rates of Asthma (per 100 Children Aged 2 to 6 Years) by Number of Significant Risk Factors

No. of Risk Factors	2 yr	3 yr	4 yr	5 yr	6 yr
Boys					
0	1.5	3.0	4.6	5.8	6.8
1	3.7	7.4	11.1	14.0	16.1
2	10.5	20.2	29.1	35.7	40.1
3	29.6	50.9	66.2	75.1	80.1
Girls					
0	1.1	2.2	3.4	4.4	5.4
1	6.0	12.2	18.0	23.2	27.6

TABLE 5. Proportional Hazards Coefficients (Significance of Factor) for Models Fitted to Rates of Asthma Based on Definitions of Varying Stringency

	No. of Diagnoses Before Child Was Classified as Asthmatic				
	2	3	4	5	6
Boys					
Variable: early eczema	3.45	4.04	4.36	4.18	5.52
Significance	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Wheeze	2.39	2.79	2.66	3.89	3.40
Significance	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Parental asthma	2.78	2.90	3.21	3.21	3.63
Significance	$P < .001$	$P < .001$	$P < .001$	$P < .001$	$P < .001$
Rate of asthma	14.3%	11.3%	8.6%	7.3%	6.0%
Girls					
Variable: early eczema	5.80	5.06	3.99	4.20	—*
Significance	$P < .001$	$P < .01$	$P < .05$	$P < .05$	
Rate of asthma	6.3%	4.4%	3.4%	2.5%	2.3%
Overall rate of asthma	10.3%	7.8%	5.9%	4.8%	4.2%

* The number of subjects with asthma was insufficient to estimate coefficient.

ing definitions of the condition. For the total cohort, the rate to age 6 years was 10.3% if two or more episodes was used as the basis of the classification and reduced to 4.2% if six or more episodes was used as a criterion. (2) For boys, the proportional hazards coefficients for each risk factor show a clear tendency to increase as the definition of asthma becomes more stringent. This result is to be anticipated as one would expect that as the severity of the child's asthma increased, the discriminatory power of the risk factors would increase. However, for girls, there is a decline in the values of the proportional hazards coefficients, suggesting that as the stringency of the definition of asthma increased, there was decreased predictive power. The reasons for this are not entirely clear, but it seems possible that the decline in the proportional hazards coefficients reflects the fact that very few girls suffered a significant number of asthmatic attacks, and it is possible that the small numbers studied may have influenced the stability of the proportional hazards coefficients. (3) In any event, the analysis shows that irrespective of the stringency of the definition of asthma, the same constellation of risk factors emerges as being associated with the condition, and, accordingly, it is unlikely that the conclusions drawn in this study can be ascribed to the way in which asthma was defined.

In addition, there has been some debate as to whether wheezy bronchitis and asthma are distinct conditions. To examine the effects of including or excluding diagnoses of wheezy bronchitis from the definitions of asthma, the results were re-analyzed excluding all diagnoses of wheezy bronchitis. As might be expected from the fact that only 8% of all diagnoses were for wheezy bronchitis, the results

did not differ depending on whether wheezy bronchitis was included or excluded from the definition.

DISCUSSION

This longitudinal study suggests that a substantial proportion of children had been determined to be suffering from one or more episodes of asthma or wheezy bronchitis by age 6 years. Depending on the stringency of the criteria used to define the child as asthmatic, the proportion of children classified as asthmatic ranged from 10.3% (for those with two or more episodes) to 4.2% (for those with six or more episodes). Despite the fact that the prevalence and incidence of asthma varied with the stringency of definition of the condition, the risk factors associated with asthma remained invariant.

The most notable aspect of the findings was the way in which the child's sex influenced not only the risk of asthma but also the factors that were associated with the condition. Boys had more than twice the rate of asthma; this finding is in agreement with several other reports.^{4,7,12,13,17} In addition, the factors associated with the development of asthma in boys differed from those associated with the development of asthma in girls. For boys, parental asthma, early eczema, and wheeze in the first year were significant risk factors. For girls, the only significant risk factor was early eczema. These trends were reflected in the predictability of the condition: it was possible to identify boys with risks of asthma as high as 80% by age 6 years and as low as 7%; by comparison, the prediction of asthma for girls was modest.

The pervasive influence of the child's sex on both the prevalence and correlates of early asthma could suggest that asthma is a sex-limited or sex-influ-

enced condition. However, the possibility has been considered in a previous report on this cohort and a more likely explanation would seem to be that the condition is sex-expressed, with genetically susceptible boys expressing their asthmatic tendencies at the earlier age than genetically susceptible girls.⁷ This hypothesis would also account for the changing sex ratios that have been observed in childhood asthma; the condition is more common in boys in early and middle childhood and equally frequent in both sexes in later childhood.^{4,5}

It has been long assumed that asthma is related to some generalized tendency to atopic disease so that conditions such as asthma, eczema, and allergic rhinitis tend to run in families.⁴⁶ The findings of this and a previous study⁷ suggest that this conclusion is an oversimplification inasmuch as detailed analysis of family resemblance in asthma and eczema for this cohort has suggested the presence of three quite distinct components of "inheritance": (1) an asthma-specific tendency whereby asthma in parents is associated with asthma in the child; (2) an eczema-specific tendency whereby eczema in the parents is associated with eczema in the child; and (3) a generalized atopic tendency for both asthma and eczema to occur together. These findings, coupled with the way in which asthma is influenced by the child's sex, suggest the presence of a complicated and at present poorly understood mode of inheritance which cannot be summarized by the unitary concept of atopy.

Several authors¹³⁻¹⁶ have suggested that early viral respiratory infection may predispose children to develop asthma. The findings of our study provide only weak support for this view. Overall, there was no association between the rate of respiratory illness during early life and asthma. However, it is possible that this finding is misleading because it may be that only specific types of viral infection predispose children to develop asthma and accordingly one might not expect to find a strong association between overall rates of respiratory illness and subsequent asthma. Unfortunately, it was not possible in this study to classify respiratory illness on the basis of the source of the infection. The correlation between early wheeze and subsequent asthma might suggest a common source of viral infection which predisposes children to wheeze during early life and to develop subsequent asthma, but at the same time it is also possible that the association may simply reflect the difficulties of diagnosing asthma during infancy and that the children who were described as wheezy were merely manifesting the first stages of later asthma.

It has been held that risks of asthma and other forms of atopy can be reduced by exclusive breast-

feeding.^{9,22-24,47-50} However, in this and several previous studies of the cohort,³³⁻³⁵ we have been unable to demonstrate benefits for breast-feeding in the reduction of atopic disease. Moreover, the view that breast-feeding prevents atopy has come under criticism recently with many studies reporting no effect or in some cases increases in atopy among breast-fed children.^{33-36,51-54} It is notable that in this study, breast-fed boys had higher rates of asthma than other children, although this difference did not reach statistical significance. Although the role of breast-feeding in the prevention of asthma and other forms of atopy remains controversial, it may be fairly claimed that it is unlikely that infant feeding patterns make a major contribution to variability in the risk of asthma or eczema in the child population. However, as we have noted previously it is possible that highly selected subgroups of children may benefit from breast-feeding.³⁵

It has been suggested that cigarette smoking may trigger or exacerbate attacks in patients suffering from asthma,²⁵ and this has led to the speculation that parental smoking may lead to the development of asthma in children.⁹ However, we were unable to find any effect for parental smoking on rates of asthma and this confirms the findings of a previous longitudinal study.⁹ On the other hand, Gortmaker et al.²⁶ did find a small but statistically significant tendency for the rate of asthmatic attacks to be higher in families in which parents smoked. Collectively, these findings suggest that although parental smoking may increase the risk of asthmatic attacks, it is not implicated in the etiology or development of the condition. In previous studies of this cohort,^{37,38} we have found an association between parental smoking and lower respiratory tract infection in children, and it would appear in confirmation of the conclusion of Leeder et al.⁸ that although parental smoking may play a role in increasing susceptibility to lower respiratory tract infection, it does not appear to be implicated in the development of asthma in early childhood.

It has often been suggested that asthma is a psychosomatic illness triggered or caused by various social or personality factors. Recently, this view has fallen into some disrepute and there have been a large number of criticisms of the theory that asthma is a psychosomatic condition.^{18,19} Our study indicates that stress in the family is not related to the development of childhood asthma and this coupled with the contradictory and confused findings on both childhood psychopathology and abnormal parenting among asthmatic children tends to support the conclusions of Werry¹⁹ that there is no good evidence that asthma is necessarily a psychosomatic disease. In a previous study of this cohort,³²

we have been able to show that a series of conditions including lower respiratory tract illness, gastroenteritis, and accidents are influenced by family stressors. The fact that a similar finding does not hold for asthma casts further doubt on the alleged psychosomatic basis of the condition.

Family social background and related factors were unrelated to risks of asthma in early childhood. This result is not entirely consistent with previous findings that New Zealand Polynesian children have a greater risk of asthma than white children.^{30,31} The reasons for this difference are not clear, but it is possible that it arises from the age of the children being studied or from the fact that the majority of children nominally classified as Polynesian in this study had 25% or less Polynesian ancestry.³²

Asthma afflicts a significant minority of the child population and its etiology is poorly understood. The search for social and familial correlates has led to a large and uneven research literature, suggesting the way in which various social and environmental factors may contribute to the development of asthma. This 6-year prospective study indicates that early childhood asthma appears to be inherited to some extent, its age of expression is related to the child's sex, and it has a complex interaction with other forms of allergic disease.⁷ It is not related to infant feeding practices, smoking in the family, the presence of pets in the house, stress in the family, or the family's general social or economic situation. This is not to say that in individual cases these factors may not play a role in the development and onset of asthma, but rather that their role in contributing to the overall variations in the rate of the condition in the general child population (at least during early childhood) appears to be negligible. This would suggest that the etiologic basis of asthma is more likely to be found in studies of the genetic, physiologic, and immunologic basis of the condition rather than through an examination of the structure, practices, or dynamics of the family of the asthmatic child.

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ARE INTENSIVE CARE UNITS FUTILE?

[An] expert who worked for five years at a hospital in Cali, Colombia, told how the low-weight newborn mortality rate dropped greatly after an intensive care unit with all of the necessary equipment and trained personnel was opened at his hospital.

"But then we did a follow-up study to see what happened after the babies went home," he said "and we discovered that 75% of the infants were dead in six months from infections and malnutrition."

Submitted by Student

From Nelson H: Colombians 'pack' infants to mothers. *LA Times*, April 3, 1984.

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2023380637

Murray, A.B., Morrison, B.J. "The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma" J Allergy Clin Immunol 77(4): 575-581, 1986.

ABSTRACT. The effect of parental smoking was assessed in 94 consecutively observed children, aged 7 to 17 years, who had a history of asthmatic wheezing. The 24 children whose mothers smoked, when they were compared with children whose mothers did not smoke, had 47% more symptoms, a 13% lower mean FEV1 percent, a 23% lower mean FEF25-75%, and fourfold greater responsiveness to aerosolized histamine. A dose response was evident. There was a highly significant correlation between the results of the tests and the number of cigarettes the mother smoked while she was in the house. The differences between the children of smoking and nonsmoking mothers were greater in older than in younger subjects. The smoking habits of the father were not correlated with the severity of the child's asthma.

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The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma

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The effect of parental smoking was assessed in 94 consecutively observed children, aged 7 to 17 years, who had a history of asthmatic wheezing. The 24 children whose mothers smoked, when they were compared with children whose mothers did not smoke, had 47% more symptoms, a 13% lower mean FEV₁, percent, a 23% lower mean FEF₂₅₋₇₅, and fourfold greater responsiveness to aerosolized histamine. A dose response was evident. There was a highly significant correlation between the results of the tests and the number of cigarettes the mother smoked while she was in the house. The differences between the children of smoking and nonsmoking mothers were greater in older than in younger subjects. The smoking habits of the father were not correlated with the severity of the child's asthma. (J ALLERGY CLIN IMMUNOL 77:575-81, 1986.)

Although cigarette smoke from parents is believed to increase wheezing among their children,¹ results from different surveys have been conflicting. In some studies parental smoking has no apparent effect²⁻⁵; in

Abbreviations used

FEF₂₅₋₇₅: Maximal midexpiratory flow rate between 25% and 75% of FVC
PC₂₀: Provocation concentration of histamine causing a 20% fall in FEV₁

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other studies greater frequency of wheezing is observed only if the mother smokes⁶; in yet other studies the prevalence of wheezing increases with the number of parents that smoke.⁷ Similarly, spirometric values

TABLE I. Comparability of groups

Features	Mother Nonsmoker	Mother Smoker	p Value (two-tailed)
	n = 70	n = 24	
Mean age (yr)	11.1	10.8	0.77
M:F ratio	21:14	19:5	0.15
Previous surgical operation ^a	27 (42%)	8 (38%)	0.94
More than three colds per year ^b	22 (49%)	9 (56%)	0.87
Gas stove in the kitchen ^c	6 (12%)	2 (8%)	0.94
Dog or cat present	26 (49%)	11 (58%)	0.69
Any skin test positive	55 (79%)	21 (87%)	0.51
Mean diameter wheal to <i>D. farinae</i> (mm)	2.3 ± 0.4	1.6 ± 0.6	0.85

^aNine subjects were omitted from the analysis because of missing data.^bThirty-three subjects were omitted from the analysis because of missing data.^cTwenty subjects were omitted from the analysis because of missing data.

are variously reported as unaffected^{2, 6} or as slightly decreased, although significantly,^{5, 7-9} when parents smoke.

These epidemiologic surveys have all been carried out on large representative groups of children. Because of this method of selection, those most likely to be affected by the smoke, the ones with asthma, were in the minority. In order to assess the effect of passive smoking on these more susceptible subjects, we examined a group of children who had a history of asthma or wheezing. Histamine bronchial challenge was performed in addition to spirometry because adults who themselves smoke may have increased bronchial responsiveness.^{10, 11} Consequently, we suspected that children who are passive smokers might also have more irritable bronchi, resulting in an exacerbation of their wheezing.

METHODS

The study population consisted of 94 children, aged 7 to 17 years, who were referred consecutively to one of the authors for evaluation of suspected allergic disease and who had a history of wheezing or asthma. A trained interviewer asked the following standardized questions of the accompanying parents about the child's illness during the past 12 months: the frequency of wheezing; the frequency with which bronchodilator medications had been administered; whether or not corticosteroid tablets or corticosteroid aerosols had been used; and whether the child wheezed on exertion. Each feature in the history was assigned a range of scores; the scores for each individual were added to produce a summary rating called an asthma history score.¹² Children with no symptoms or medication for asthma during the previous year, for example, had a score of 0, and children with the most severe asthma had a summary score of 14 (Appendix). Inquiry was also made about other factors. The interviewer asked whether there was a gas cooking stove in the home, a device whose fumes might be irritating

to the bronchi; whether there was a dog or a cat in the house, animals whose emanations might cause sensitization; whether the child had had a surgical operation, since the frequency of such a procedure might indicate the readiness with which the parents sought and followed medical advice; the number of colds in the past year, since respiratory infections themselves may precipitate and worsen asthmatic attacks; and, finally, the parents were asked how many cigarettes, cigars, and pipefuls of tobacco they smoked, both inside and outside the house. The child was asked privately whether or not he or she smoked.

Forced expiratory spiogram

Forced expiratory maneuvers were performed until there were three in which the FVC agreed within 5%. This was always achieved within five efforts. The tracing that had the greatest sum of FVC and FEV₁ was used for all measurements.¹³ The FVC, FEV₁, and FEF₂₅₋₇₅ were expressed as a percentage of predicted mean for age, sex, and height.¹⁴

The spiogram was recorded with a Pulmonor (Jones Medical Instrument Co., Oak Brook, Ill.) waterless spirometer that was calibrated weekly with a known volume of CO₂ discharged at a standard velocity from a calibrator instrument. The results of the tests were analyzed and printed by a Datamatic (Jones Medical Instrument Co.) computer that was connected to the spirometer.

Bronchial reactivity to histamine

Two days before the appointment, the parents were instructed to stop antihistamines and theophyllines and to administer no other bronchodilator medications for the 8 hours immediately before the visit, if it was possible. They were unable to stop medication in 23.1% subjects. A bronchial challenge test was not performed on these children nor on the children who reported a respiratory infection during the preceding 2 weeks, had an FEV₁ < 60% predicted or below 1 L in volume, or were themselves smokers. The test was performed on the day on which they were first observed in all of the remaining 41 subjects.

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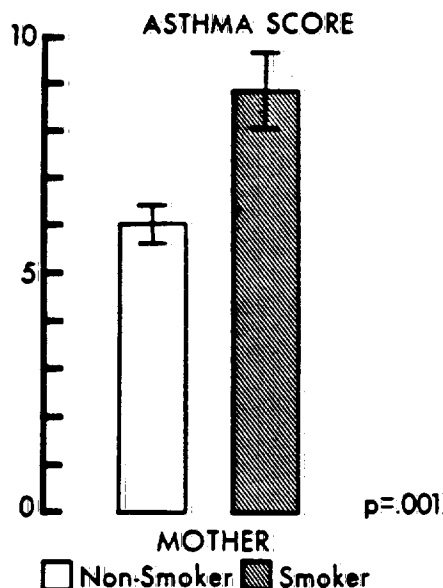


FIG. 1. The asthma history severity score, which ranges from a minimum of 0 to a maximum of 14, in two groups of children with a history of wheezing. The mothers of 69 were nonsmokers, and mothers of 23 were smokers. Means \pm standard errors are presented.

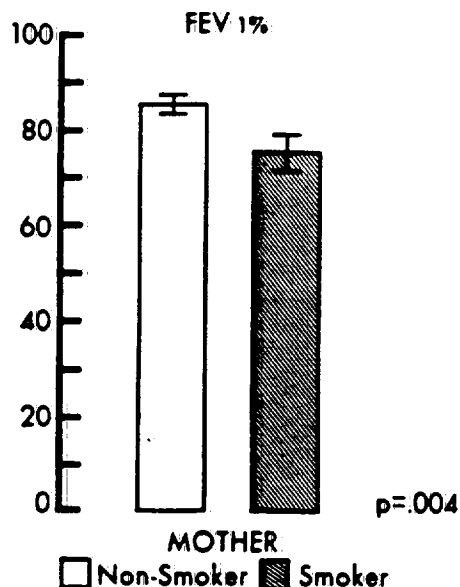


FIG. 2. The FEV₁ percent predicted in two groups of children with a history of wheezing. The mothers of 70 were nonsmokers, and mothers of 24 were smokers. Means \pm standard errors are presented.

By use of a modification¹² of the method described by Cockcroft et al.,¹³ each patient was administered doubling concentrations of histamine acid phosphate aerosol by mask, each inhalation session lasting for 2 minutes until PC₂₀. The strongest concentration administered was 8 mg/ml. Children whose FEV₁ did not decrease by 20% when this concentration was administered were deemed, for the purpose of calculating the mean PC₂₀, to respond to double that concentration, i.e., 16 mg/ml of histamine acid phosphate. There were two such subjects. The mothers were both non-smokers.

Skin prick tests

By use of a standard method,¹⁴ skin prick tests were performed on all subjects with negative and positive (histamine) control solutions, with 10% cigarette smoke (Bencard Division of Beecham Laboratories, U. K.), and with extracts of common inhalant and pollen allergens. The diameter of each resulting wheal was measured. If any wheal was 2 mm greater than that of the negative control solution, the test was regarded as positive and the patient as atopic. A 1% extract of *Dermatophagoides farinae* was included among those solutions tested, since the result would, if it were positive, be evidence not only of atopy but also of exposure to larger than usual numbers of house dust mites.¹⁵

The spirometric, bronchial challenge, and skin tests were performed by a technician who was unaware of the family's smoking habits.

Statistical method

Standard *t* tests were used to test differences between all quantitative variables except for those that were on a percentage scale, in which case a test of difference between normally distributed variates was applied. Pearson product-moment correlation coefficients were calculated as a measure of association.

RESULTS

The children were divided in the analysis into two groups on the basis of whether the mother did or did not smoke. These groups were comparable for age, gender, exposure to airborne irritants and allergens, percent that had had surgical operations, percent with frequent colds, proportion of subjects with atopy, and degree of sensitivity to house dust mites (Table I). The above mentioned variables were also comparable when the population was divided according to whether their fathers did or did not smoke.

Children of mothers who smoked had increased bronchial reactivity and worse asthma. Children whose mothers smoked had, on average, 47% more symptoms (Fig. 1), a 13% lower FEV₁ (Fig. 2), a 23% lower FEF₂₅₋₇₅ (Fig. 3), and a fourfold greater responsiveness to aerosolized histamine (Fig. 4). All these differences between the two groups were highly significant (Table II). When the mean FVC percent

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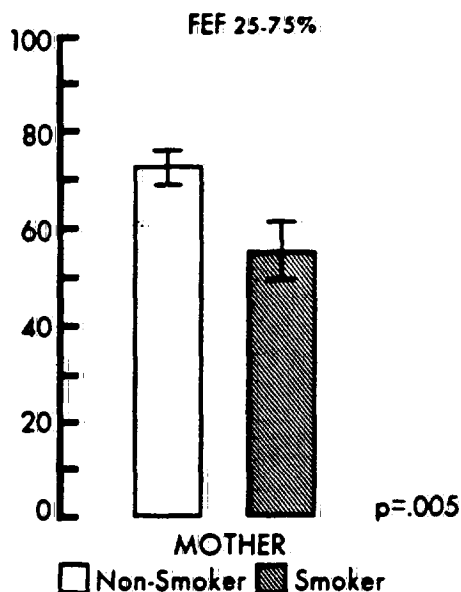


FIG. 3. The FEV₂₅₋₇₅ percent predicted in two groups of children with a history of wheezing. The mothers of 70 were nonsmokers, and mothers of 24 were smokers. Means \pm standard errors are presented.

predicted was examined, it was found not to be significantly different when the whole group of 94 subjects was considered. However, it was different in the subgroup of 41 subjects on whom the PC₂₀ was performed, i.e., subjects whose values were not influenced by recent bronchodilator medications or by respiratory infections. In this subgroup, the FVC was $85.2 \pm 2.7\%$ in children of mothers who smoked and $97.5 \pm 18\%$ in children of mothers who did not smoke ($p = 0.002$). We were therefore able to demonstrate a significant difference between the two groups in all tests of asthma severity that were applied.

A dose response to the mothers' cigarette smoke is also apparent both in the whole group of 94 and in the subgroup of 41 subjects. There was a significant correlation between the logarithm of the number of cigarettes the mother smoked while she was in the home and FVC, FEV₁, FEV₂₅₋₇₅, asthma history score, and bronchial responsiveness to histamine (Table III). Not only was the correlation with bronchial responsiveness significant when all subjects with a baseline FEV₁ of 60% or more were included, but it remained significant ($p = 0.001$) when the analysis was restricted to subjects with a baseline FEV₁ of more than 70% predicted, the level usually accepted for histamine bronchial challenge testing.¹⁵

The effect of maternal cigarette smoke appears to be greater in older than in younger children, sug-

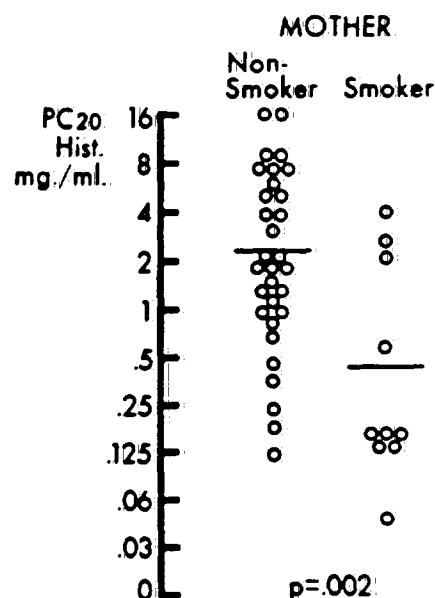


FIG. 4. The PC₂₀ in two groups of children with a history of wheezing. The mothers of 32 were nonsmokers, and mothers of 10 were smokers.

gesting that not only the daily number of cigarettes, but also the years of passive smoking increases the severity of its adverse effects. In children more than 11 years of age, there is, for example, a 19% difference in mean FEV₁ between the two groups, whereas in less than 11 years of age, the difference is only 9% (Table IV). Bronchial responsiveness in the older and younger subgroups could not be compared because it was assessed in only three of the older group whose mothers were smokers.

By contrast with the strong correlation between the mother's smoking habits and the severity of her child's asthma, there was no correlation between the number of cigarettes, cigars, or pipes of tobacco that the father smoked in the house and measures of lung function in the child (Table III), nor did the simple distinction of whether the father smoked or not smoked have any significant effect on any of the measurements (Table II). A partial explanation for the absence of effect may be the smaller number of cigarettes smoked at home by the father compared with the mother. Although the mean total of cigarettes that fathers smoked per day, 23, was slightly larger than that smoked by mothers, 18, the mean number that fathers smoked while they were in the house, eight, was significantly smaller than the number smoked in the house by mothers, 13.

Since there appeared to be no relationship between the smoking habits of the father and the severity of

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TABLE II. Difference in indicators of asthma severity between groups distinguished by smoking habits of the parents

	History score*	FEV ₁ , percent predicted	FEF ₂₅₋₇₅	Geometric mean PC ₂₀ †	
Mother					
Nonsmoker (n = 70)	6.0 ± 0.4	85.5 ± 1.8	72.3 ± 2.8	2.2	n = 31
Smoker (n = 24)	8.8 ± 0.8	74.4 ± 3.7	55.6 ± 5.6	0.46	n = 10
P Value (two-tailed)	0.001	0.004	0.005	0.002	
Father					
Nonsmoker (n = 64)	6.9 ± 0.5	81.9 ± 2.1	67.0 ± 3.1	1.7	n = 26
Smoker (n = 28)	6.4 ± 0.6	84.4 ± 2.9	70.5 ± 4.9	1.2	n = 15
p Value (two-tailed)	0.5	0.5	0.5	0.4	
Parents					
Both nonsmokers (n = 51)	6.2 ± 0.5	84.7 ± 2.1	71.6 ± 3.2	3.1	n = 21
Either smokes (n = 43)	7.4 ± 0.6	80.3 ± 2.7	63.8 ± 4.3	0.8	n = 20
p Value (two-tailed)	0.11	0.2	0.15	0.001	

Means ± standard errors are presented.

*History score available for 92 children.

†PC₂₀ measured on all 41 children who were eligible for the test. T tests were carried out on logarithm of the PC₂₀ values.**TABLE III.** Correlation (r) between indicators of asthma severity and the logarithm of the number of cigarettes smoked in the house by the parents and the probability (p) of r ≠ 0

	FVC (% Predicted)	FEV ₁ (% Predicted)	FEF ₂₅₋₇₅ (% Predicted)	Log (PC ₂₀)	History score
Mother	r = 0.186	-0.300	-0.280	-0.482	0.224
	p = 0.039	0.002	0.004	0.001	0.018
Father	r = 0.036	0.028	0.001	0.075	0.084
	p = 0.367	0.395	0.495	0.319	0.218
Both parents	r = -0.081	-0.200	-0.227	-0.460	0.136
	p = 0.228	0.031	0.017	0.001	0.107

the child's asthma, the influence of both parents smoking, considered together, was less than that of only the mothers smoking (Table II).

The prevalence of smoking among the children was low. Only two of them admitted to being smokers. The mother of the one smoked, and the mother of the other did not. The skin prick test to cigarette smoke was negative in all subjects.

DISCUSSION

We found, in a series of unselected consecutively referred children with wheezing, that asthma was more severe if the mother was a smoker. The decreases in spirometric values that we observed were larger than any previously reported. In these other studies, the decrease in mean values, although the decrease was significant in some children, did not exceed 5% in any of the children.¹ Vedal et al.,⁸ for example, detected a 3% reduction in mean FEF₂₅₋₇₅ in children whose mothers smoked. We found a 23% reduction.

Our results were also more consistent. With every test used we found a significant difference between those whose mothers did and did not smoke. Previous studies have found a significant difference with some tests but not with other tests. It is likely that the greater differences, which we observed, result from studying a group of children who have asthma rather than children who are representative of the population at large. An additional new finding in our study was that the child's bronchial responsiveness increased if the mother was a smoker.

The evidence suggests that it is airborne cigarette smoke that causes the adverse effect. Not only is there a strong association between maternal smoking and severity of the child's asthma, but there is also evidence of a dose response. We found a significant correlation between all indicators of asthma severity and the logarithm of the number of cigarettes the mother smoked while she was in the home. There was also evidence that length of exposure had an effect. The

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TABLE IV. Differences in indicators of asthma severity between groups distinguished by age and by smoking habits of the mother

	History score*		FEV ₁ % predicted		FEF ₂₅₋₇₅ predicted		Geometric mean PC ₂₀ †	
	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)	Age (>11 yr)	Age (<11 yr)
Mother Nonsmoker	6.6 ± 0.5	5.3 ± 0.6	84.5 ± 2.8	86.7 ± 2.2	73.6 ± 4.1	70.8 ± 3.7	2.3 n = 20	2.1 n = 11
Mother Smoker	10.1 ± 0.9	7.8 ± 1.2	68.7 ± 6.4	79.2 ± 4.0	52.0 ± 10.5	58.6 ± 5.6	0.4 n = 3	0.5 n = 7
p Value (two-tailed)	0.005	0.07	0.04	0.12	0.07	0.08	0.06	0.02

Forty-eight subjects were aged 11 years or older, and 46 were younger than 11 years. Means ± standard errors are presented.

*The history score was available for 92 children.

†The PC₂₀ was measured on 41 subjects.

older children, who had presumably been exposed to cigarette smoke for more years than the younger ones, were more severely affected. This finding is similar to that of Tager et al.¹⁸ They reported that the normal rate of increase in FEV₁ during adolescent growth is slowed in children whose mothers smoked. Further evidence, that it is passively inhaled smoke that is responsible for the changes, is the effect observed when the mother stops smoking. Vedal et al.⁸ report that children whose mothers are current smokers do but children whose mothers are exsmokers do not have significant differences in pulmonary function from those whose mothers are nonsmokers.

In contrast to the smoking habits of the mother, those of the father had no significant correlation with the severity of the child's asthma. These findings agree with those in more recently published large epidemiologic studies.^{8,9} Several factors may account for this apparent paradox. One is our finding that the father, compared with the mother, smokes significantly fewer cigarettes when he is at home. Another is the possibility that the mother, more frequently than the father, is in the same room as the child when she smokes a cigarette. A third possibility is that the number of cigarettes smoked in the house are more accurately reported for the mother than for the father. The mother was usually the person who gave the information. Whatever the reason, the father's smoke did not appear to influence the child's asthma significantly. When we examined the effect of maternal and paternal smoking together, therefore, we found it to be less clear than when we examined the result of maternal smoking alone. This observation may explain the lack of effect of parental smoking on wheezing and spirometric values reported in some epidemiologic studies.^{2,3,6}

It appears unlikely that greater exposure to respiratory infections or allergens was responsible for the

increased severity of asthma in children whose mothers smoked. Comparable proportions in both groups had frequent colds, had a cat or a dog in the house, and had a positive skin test to an inhalant allergen. Furthermore, the skin prick test reaction to *D. farinae* was smaller, if anything, in the group whose mothers were smokers, and it did not appear that the mothers who were nonsmokers more readily sought medical advice for their children than did those who were smokers. The frequency of surgical operations was similar in the two groups; however, this possibility could not be excluded.

Why cigarette smoke should increase asthmatic symptoms is not known. One possibility is that bronchial epithelium is damaged, irritant receptors are stimulated, and bronchial responsiveness is increased.¹⁹ Another possibility is that a specific allergen in tobacco leaf or smoke may be responsible. Lehrer et al.²⁰ explored this possibility but found no association between clinical symptoms from smoke and positive skin prick tests, precipitating antibodies, or specific IgE to tobacco smoke. Similarly, in our study, all skin prick tests to smoke were negative, but these findings do not exclude the possibility that the adverse effect of cigarette smoke is immunologically mediated. Two observations suggest that it may be. One is the presence of abnormally high IgE reported in adults who smoke²¹ and in the children of smokers²² and the other is an increased bronchial responsiveness, both in healthy adults who are smokers^{10,11} and in our study population of children with asthma whose mothers were smokers. Increased responsiveness of the bronchi often results after the lung has been the site of an allergic reaction.²³ Burrows et al.²⁴ suggest ways, other than acting as a common inhalant allergen, in which tobacco smoke may elicit an allergic reaction in the lung.

Our findings indicate that maternal smoking aggra-

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vates asthma in children, the effect being clinically important as well as statistically significant. Paternal smoking was not related to the severity of the child's asthma, but a possible explanation for this is that most of the father's cigarettes are smoked when he is away from home. Physicians who observe children with asthma should ask the parents if they smoke. Parents that do smoke should be advised to stop smoking, at least when they are in their house.

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APPENDIX

History	Asthma history score*				
	0	1	2	3	4
Severity, parents assessment	None	Mild	Moderate	Severe	—
Days of wheeze	None	1 to 3	4 to 182	182 to 365	—
Days of medication	None	1 to 3	4 to 30	31 to 182	183 to 365
Corticosteroid medication	None	—	—	Yes	—
Wheeze on exertion	None	Yes	—	—	—

*Numerical score indicating severity assigned to each feature in the history.

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Anderson, H.R., Bland, J.M., Peckham, C.S. "Risk Factors for Asthma up to 16 Years of Age" Chest 91(6): 127S-130S, 1987.

SUMMARY: From a national cohort of 8,806 children examined at ages seven, 11 and 16 years (National Child Development Study), data on asthma or wheezing illness (AW) were analyzed to describe its natural history in childhood and its risk factors. Factors found to predict the subsequent onset of asthma included male sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy/adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks. A wide range of perinatal factors, including feeding practices, and social and family factors were shown to have no effect on natural history.

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Risk Factors for Asthma up to 16 Years of Age*

Evidence from a National Cohort Study

H. R. Anderson, M.D.; J. M. Bland, Ph.D.; and
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From a national cohort of 8,806 children examined at ages seven, 11 and 16 years (National Child Development Study), data on asthma or wheezing illness (AW) were analyzed to describe its natural history in childhood and its risk factors. Factors found to predict the subsequent onset of asthma included male sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy/adenoidec-tomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks. A wide range of perinatal factors, including feeding practices, and social and family factors were shown to have no effect on natural history.

Much of the existing epidemiologic evidence about the etiology of asthma rests on prevalence and follow-up studies and there is a serious lack of population-based cohort data. The National Child Development Study (NCDS) originated in the National Perinatal Study¹ and went on to become a multipurpose cohort study of child development including health. While it was not designed specifically to study the epidemiology of asthma, it is nevertheless possible to obtain valuable information relating to the natural history of asthma. This article describes some of the findings from our analysis of NCDS data which have implications for the etiology of asthma.

MATERIALS AND METHODS

The NCDS followed-up at ages seven, 11 and 16 all children in England, Scotland and Wales born during one week of March, 1958. At each follow-up, information about current or past asthma or wheezing illness was obtained as part of a structured questionnaire on medical and other topics administered to parents by health visitors. The wording of the asthma questions varied at each interview but it was nevertheless possible to classify subjects at each interview into three categories: no asthma or wheezing, previous asthma or wheezing but not in the past 12 months, and current asthma or wheezing (symptoms reported in the past 12 months). Based on these three possibilities at each of three interviews, 27 mutually exclusive natural history categories can be created. Some of these contain small numbers or are of limited clinical or epidemiologic interest, and so for the purpose of the present analysis a collapsed classification of six natural history categories was used.

These natural history categories were analyzed in relation to medical and social data collected at each of the follow-up medical examinations and home interviews. Factors that have previously been reported to be associated with asthma or wheezing were selected together with those considered likely to influence the natural history of asthma.

The overall association between a variable and the natural history category was tested using the Chi-squared test or one-way analysis of variance as appropriate. Where there was a statistically significant

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Table 1—Lifetime Incidence of Asthma or Wheezing (n = 8,806)

Age at interview (yrs)	Asthma or wheezing at any time in past (percent)	
	Cross-sectional	Cumulative*
7	18.3	18.3
11	12.1	21.9
16	11.6	24.7

*Using information from previous interviews

Table 2—Prevalence of Asthma or Wheezing in 12 Months Preceding Interview (n = 8,806)

Age at interview (yrs)	Asthma or Wheezing in past 12 months (percent)	
	Cross-sectional	Cumulative*
7	8.3	8.3
11	4.7	10.7
16	3.5	11.1

*Using information from previous interviews

overall association, the relative risks of each natural history category were calculated. The statistical significance of the relative risk was tested by calculating 95 percent confidence intervals.

RESULTS

Data on asthma or wheezing were obtained at all three ages for 8,806 of the original NCDS cohort of over 15,000 children living in England, Scotland and Wales and available for follow-up at seven years.

The reported lifetime incidence of asthma or wheezing is shown in Table 1. Using data from all three interviews, a total of 24.7 percent of children had experienced asthma or wheeze by the age of 16 years. When questioned at age 16 years, however, the proportion reporting past asthma or wheeze was less than half this figure (11.6 percent). The prev-

Table 3—Prognosis of Asthma or Wheezing if Current (past 12 months) at Age 7 (n = 731)

Persistence of AW and age (yrs)	Percent of 7 year-olds who reported current AW
Current at 11	25.3
Current at 16	16.3
Current at 11 and 16	10.5
Current at 11 or 16	34.1
Not current at 11 or 16	65.9

Table 4—Natural History Categories (n = 8,806)

Category	Percent of sample
Never had asthma or wheezing	75.3
Onset before age 7 but not current at 7 or reported subsequently	8.6
Current at age 7 but not reported subsequently	5.5
Onset age 0 to 7 and also reported at 11 or 16	4.2
Onset age 8 to 11	3.6
Onset age 12 to 16	2.8

Table 5—Factors Predicting the Onset of Asthma or Wheezing

Predictive factors	Overall χ^2 P value	Relative risk of:	Natural history				
			By age 7 not after	At age 7 not after	Age 0-7 and after	Age 8-11 onset	Age 12-16 onset
Perinatal							
Sex of child	<0.001	Boy: girl	1.1	1.2	1.4*	1.3*	1.4*
Mother's age	<0.001	15-19: 20-29 yrs	1.4*	1.5*	1.1	1.9*	1.7*
		15-19: 30+ yrs	1.6*	1.3	1.3	1.9*	2.0*
		20-29: 30+ yrs	1.2	0.9	1.1	1.0	1.2
Smoking in pregnancy	<0.001	Smoker: Non-smoker	1.3*	1.2	0.8	1.0	1.0
Region of child's birth	<0.01	North: Centre	0.7*	0.9	0.9	0.7	1.0
		North: South	0.8*	0.9	1.0	0.9	1.0
		Centre: South	1.1	1.0	1.0	1.2	1.0
Assessed at 7							
History of pneumonia	<0.001	Yes: No	2.0*	2.0*	4.3*	1.5	1.8*
Tonsillectomy/ adenoidectomy	<0.001	Yes: No	1.3*	1.2	1.2	1.2	1.4*
Eczema in 1st year	<0.001	Yes: No	1.2	1.4	5.4*	1.7*	1.5
Eczema after 1st year	<0.001	Yes: No	1.1	1.3	4.7*	1.3	1.7*
Eczema on Dr. exam.	<0.001	Yes: No	0.8	1.1	4.9*	1.6	2.1*
Hayfever or sneezing ever	<0.001	Yes: No	1.3	2.0*	7.1*	1.5	1.7*
Periodic vomiting or bilious attacks ever	<0.001	Yes: No	1.2*	1.4*	1.8*	0.8	1.4*
Periodic abdominal pain ever	<0.001	Yes: No	1.4*	1.3*	1.5*	0.9	1.4*
Assessed at 11							
Whooping cough ever	<0.001	Yes: No	1.2*	1.3*	1.4*	1.4*	1.4*
Eczema in past year	<0.001	Yes: No	1.2	1.2	4.2*	1.9*	1.7*
Hayfever or allergic rhinitis in past year	<0.001	Yes: No	1.0	1.2	5.2	2.2*	1.9*

*P<0.05

absence of current asthma was highest at seven years (8.3 percent) but had fallen to 3.5 percent at 16 years (Table 2). At each interview, the lifetime and current rates for the present cohort (those with data available at all interviews) were similar to those among subjects interviewed only once or twice. Of those with current symptoms at seven, 28 percent reported current symptoms at 11 years, 16 percent at 16 years and 11 percent at both ages (Table 3).

For the purpose of analysis, the 27 patterns of questionnaire response were collapsed into the six categories described in Table 4.

From an etiologic standpoint two types of relationship could be discerned. In the first, a given factor was assessed prior to the onset of asthma or wheeze, and could therefore be considered predictive. In the other, the order of occurrence of the factor and the onset of asthma or wheezing could not, from the data available, be shown to be predictive because the assessment of both factors was concurrent. Most factors found to be predictive are shown in Table 5 together with their relative risks. Any concurrent associations for these variables are also shown. Of the perinatal factors the most prominent was sex of the child and the mother's age at birth of the child. Multifactorial analysis was done to explore whether social class or breast feeding might explain this latter relationship, but this was not the case.

Of the factors assessed at seven or 11 years, the main ones predicting subsequent onset of asthma or wheezing were atopic conditions—eczema or allergic rhinitis—and (at

seven years only) periodic vomiting or abdominal pain. A history of pneumonia (at seven years) and whooping cough (at 11 years) were also predictive. Previous tonsillectomy or adenoidectomy reported at age seven years predicted onset in adolescence (though not when reported at 11 years).

Those factors which were concurrently associated with asthma or wheezing but not predictive are shown in Table 6. They mainly comprise upper and lower respiratory conditions but also include fits or convulsions in the first year (but not continuing into later life), enuresis, headaches and one adverse socioeconomic factor—sharing of one or more household facilities.

Those factors not associated with natural history are listed in Table 7. Notably, these included breast feeding, social class and a variety of indicators of socioeconomic circumstances and family stress.

Assessment of smoking in the household was inadequate, available only for the mother while she was pregnant and for both parents when the child was 16 years old. Smoking in pregnancy was associated only with an increased relative risk of asthma or wheezing during the early years of life and smoking by one or both parents reported when the child was 16 years was not related. At 16 years, the child's own smoking habit was unrelated to the presence of asthma or wheezing.

DISCUSSION

The National Child Development Study was not designed to examine the etiology of asthma and there are a number of

Table 6—Factors Concurrently Associated with Asthma or Wheezing but not Predictive

Concurrent factors	Overall χ^2 P value	Relative risk of	Natural history				
			By 7 not after	At 7 not after	0-7 and after	8-11 onset	12-16 onset
Assessed at 7 yrs.							
Household facilities	<0.008	Shared: not shared	1.1	1.5*	0.9	1.0	0.8
Whooping cough ever	<0.001	Yes: No	1.4*	1.2	1.4*	1.2	1.3
Throat/ear infections with fever >3 in past yr	<0.001	Yes: No	1.2	1.6*	1.4*	0.7	1.0
Running ears ever	<0.03	Yes: No	1.3*	1.3	0.9	1.0	1.2
Fits or convulsions in 1st year	<0.001	Yes: No	1.2	1.8*	2.7*	1.0	0.6
Wet by day after 3 yrs	<0.004	Yes: No	1.2	1.7*	1.0	1.5	1.2
Wet by night after 5 yrs	<0.001	Yes: No	1.5*	1.2	1.0	1.2	1.1
Assessed at 11 yrs.							
Household facilities	<0.05	Shared: not shared	1.0	1.4*	1.1	0.8	1.1
Recurrent throat/ear infections in past yr treated by Dr	<0.001	Yes: No	1.1	1.0	1.5*	1.7*	1.1
Discharging ears in past year	<0.07	Yes: No	1.2	1.3	1.8*	1.6	0.7
Tonsils/adenoids removed	<0.001	Yes: No	1.2*	1.3*	1.2	1.2	1.0
Eczema on examination (Dr.)	<0.001	Yes: No	0.8	1.1	4.9*	1.6	2.1*
Recurrent headaches or migraine past year	<0.001	Yes: No	1.2	1.1	1.6*	1.2	1.1
Recurrent vomiting or bilious attacks in past year	<0.09	Yes: No	1.0	1.5*	1.3	1.5	1.0

*P<0.05

inadequacies in the nature and timing of both the assessment of asthma and wheezing and of etiologic factors. Against this is the advantage that these data relate to a national representative sample and contain a substantial number of subjects followed-up over a long time.

By including all children with reported asthma or wheezing, however mild, the present analysis may have missed associations that relate only to more severe asthma or wheezing, which is the main concern in medical practice. The data do, however, allow a simple grading of severity and this is being analyzed at present.

Considering the logistics of such a national cohort study, the response rate for information about asthma or wheezing on all three occasions of 59 percent of the original NCDS cohort could be judged as successful. Nevertheless, this raises the possibility of bias, which has been examined in detail.² It would appear that this is unlikely to have biased our results for relative risks or incidence and prevalence estimates. At any particular age, the prevalence rates among children for whom we had linked data were similar to the rates among those not seen on each occasion. The 12-month prevalence rates observed at age seven years were similar to those of other population surveys which have included all wheezing illnesses.²²

As far as etiology is concerned, the most important findings in this study are those relating to factors which predicted or did not predict the later onset of asthma or wheezing. Among the perinatal factors, a new and possibly important finding was that the risk of all natural history categories apart from persistent asthma or wheezing (reported on all three

occasions) was increased in children of mothers who were under 20 years of age at the birth of the child. This was independent of social class or breast feeding (which were

Table 7—Factors Not Found to Be Predictive or Concurrently Associated with Asthma or Wheezing

Perinatal
Birthweight
Gestational age
Parity
Breast/bottle feeding
Birth order
Rank in family
Social class
Assessed at 7
Crowding in household
Number of children in household
Tenure of accommodation
Social class
Separation from mother
In local authority care
Absence of one or more biological parents
Previous measles
Assessed at 11
Previous measles
Social class
Assessed at 16
Age at menarche
Pubic hair rating (boys)
Smoking of child
Smoking of parents

unassociated with natural history anyway). Further analysis found that the effect of maternal age existed within the 16 to 19-year-old age group as well. This finding needs to be confirmed by other studies and we can offer no plausible theory to explain it.

The increased risk of asthma or wheezing in boys agrees with other studies,⁹ though our results differ from most in that the effect of male sex did not diminish as the age of onset of asthma increased.

The question of whether breast feeding protects against childhood asthma is of great importance since, if true, it would offer insights into etiology and a method of prevention. The evidence is patchy, but a prospective study by Blair⁹ found that asthma was more likely to persist in those who were bottle fed. Our results do not confirm this finding, nor was any other effect of infant feeding practice on natural history apparent.

The association between natural history of asthma or wheezing and other atopic conditions confirms the abundant evidence from other prevalence and case-control studies. Additionally, however, we have demonstrated that periodic abdominal pain or vomiting attacks are also predictive and that headaches or migraine are an important concurrent association, though falling just short of significance as a predictive factor. Such associations have also been observed in a separate prevalence study⁹ and can no longer be regarded as speculative. We feel that elucidation of the nature of these associations is an important research priority.

The last group of factors found to predict the onset of asthma or wheezing in adolescence were chest infections (pneumonia and whooping cough) and this finding has an important bearing on the question of whether and how early childhood chest troubles may predispose to chronic lung disease in later life as indicated in a previous prospective¹⁰ and retrospective study.¹¹

There are various explanations for the associations we have observed. The report of pneumonia or whooping cough may have been a mistaken diagnosis for what was in reality asthma. Chest infection may have led to the later onset of asthma by creating some predisposition which remained latent until adolescence. Both chest infections and asthma may have a common environmental cause or may be the result of a common predisposition via some kind of general "chesty" tendency. Perhaps the asthmatic tendency itself could predispose to chest infections and in some circumstances the chest infection might be expressed prior to the first attack of asthma.

Data about wheezing symptoms and chronic productive cough have been collected from this same cohort at the age of 23 years. Analysis of this additional information should provide further important evidence concerning the origins of both asthma and chronic bronchitis.

CONCLUSIONS

The National Child Development Study is an important source of nationally representative longitudinal data. While not specifically designed to study asthma, analysis of the data has elucidated a number of factors that predict the subsequent onset of asthma. These include male sex of the child, mother's age at child's birth, pneumonia, whooping cough, tonsillectomy/adenoidectomy, allergic rhinitis, eczema and

periodic abdominal pain/vomiting attacks.

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Occupational Asthma

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This article reviews recent developments in the study of occupational asthma and implications for the overall understanding of asthma. Occupational asthma is a clinical syndrome caused by many different agents. Contribution of studies of experimental inhalation challenges using occupational agents to the knowledge of asthmatic reactions and their mechanisms is discussed. Investigations in the occupational environment into predisposing factors and persistence or recovery after exposure to an allergic agent or nonspecific irritant are reviewed. Approaches to diagnosing asthma in the occupational environment and to assessing functional impairment and disability are outlined. Directions for future research are identified.

Studies in occupational asthma have provided considerable insight into the various etiologic factors, possible pathogenetic mechanism and, to a certain extent, the clinical course of asthma. For the purpose of this presentation, occupational asthma will be defined as asthma caused by a

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Evans, D., Levison, M.J., Feldman, C.H., Clark, N.M., Wasilewski, Y., Levin, B., Mellins, R.B. "The Impact of Passive Smoking on Emergency Room Visits of Urban Children with Asthma" Am Rev Respir Dis 135: 567-572, 1987.

ABSTRACT. Baseline data obtained from a study of 276 children with asthma from 259 low income families were analyzed to test the hypothesis that passive smoking is associated with frequency of emergency room (ER) visits, hospitalizations, and impaired pulmonary function. The data were analyzed using multiple regression techniques. We controlled for other variables that might affect the frequency of ER visits, including smoking by the children themselves and the presence of other irritants or allergens in the child's home. Passive smoking was positively associated with ER visits ($p < 0.01$), but not with hospitalizations or abnormalities in pulmonary function. The frequency of days with symptoms of asthma per month was also directly associated with ER visits ($p < 0.02$). The estimated mean annual increase in ER visits attributable to the presence of one or more smokers in the household was 1.34 ± 0.50 , an increase of 63% over nonsmoking households. The estimated annual health care cost for emergency care of children with asthma that can be attributed to passive smoking is 92 dollars (95% confidence interval from 24 to 160 dollars) for families with 1 or more smokers.

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The Impact of Passive Smoking on Emergency Room Visits of Urban Children with Asthma¹⁻³

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Introduction

Passive smoking has been associated with a variety of harmful effects on children's lungs. These include increased occurrence of respiratory illness (1-6), impaired pulmonary function (7), and increased mortality (8). In addition, passive smoking has been associated with increases in visits to the physician (8), hospitalizations (8-10), and disability days (11).

On the basis of these studies, it is logical to expect that lungs hypersensitive to irritants may be even more vulnerable to the effects of passive smoking. Because asthma is a disease characterized by airways more reactive to irritants than normal, recent investigations have explored the impact of passive smoking on morbidity and pulmonary function in patients with asthma (12-18). Although the findings do not all demonstrate impaired health, there is evidence that passive smoking has harmful effects in children and adults with asthma, including increased incidence of asthma (12), exacerbation of symptoms (13), impairment of pulmonary function (16), and increased sensitivity to histamine (18). The effect of passive smoking on health care use by children with asthma, however, has not yet been studied.

We considered it important to examine this question because of the burden that frequent emergency room (ER) visits and hospitalizations for childhood asthma place on the family and the health care system (19, 20). Our study of the impact of health education on asthma management skills of the family and emergency health care use by children with asthma (21-23) provided an opportunity to study this question. We hypothesized that there would be a direct association between smoking by family members and the frequency of the child's ER visits and acute hospitalizations for asthma. In addition, we hypothesized that passive smoking would be associated with impaired pulmonary function.

SUMMARY Baseline data obtained from a study of 276 children with asthma from 259 low income families were analyzed to test the hypothesis that passive smoking is associated with frequency of emergency room (ER) visits, hospitalizations, and impaired pulmonary function. The data were analyzed using multiple regression techniques. We controlled for other variables that might affect the frequency of ER visits, including smoking by the children themselves and the presence of other irritants or allergens in the child's home. Passive smoking was positively associated with ER visits ($p < 0.01$), but not with hospitalizations or abnormalities in pulmonary function. The frequency of days with symptoms of asthma per month was also directly associated with ER visits ($p < 0.02$). The estimated mean annual increase in ER visits attributable to the presence of one or more smokers in the household was 1.34 ± 0.50 , an increase of 63% over nonsmoking households. The estimated annual health care cost for emergency care of children with asthma that can be attributed to passive smoking is \$2 dollars (95% confidence interval from 24 to 100 dollars) for families with 1 or more smokers.

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Recognizing that factors other than passive smoking can also affect the frequency of health care use, we also explored the effect of 10 groups of variables that could influence this use (19-31). These factors, which are listed in *Appendix 1*, were included in the data analysis to control for their effect on the relationship between passive smoking and health care use as well as to identify additional variables that might be influential.

Methods

Study Population

The study sample was composed of 276 children from 259 low income families who were receiving health care for asthma in outpatient clinics at 4 New York City hospitals. Children were enrolled in the study if they met all the following criteria: a diagnosis of asthma by a physician, at least 1 wheezing episode in the previous year, at least 1 clinic visit for asthma in the previous 12 months, and age between 4 and 17 yr. Informed, written consent was obtained from the child's parent. The study was approved by the institutional committee on human research. Fifty-five percent of the children were Hispanic, 38% were non-Hispanic blacks, and 7% were white, Asian, or native American. Sixty percent of the children were male, and the mean age was 9.9 ± 0.20 yr (unless otherwise indicated, the data are reported as the mean \pm SEM). Ninety-three percent of the adult respondents to the enrollment interview were female and 67% of the households were headed by females.

Sixty-three percent of the families received public assistance.

Because no community-wide survey was conducted, we do not know how well the study sample represents the general community population of low income children with asthma served by the 4 hospitals. Preliminary results from our own survey of families who had children with asthma attending public schools in the referral area of Babies Hospital (1 of the 4 hospitals in the original study), however, suggest that children in the clinic sample used the ER more frequently and were hospitalized more often than the children in the school sample. The clinic sample averaged 2.27 ± 0.21 ER visits per year, whereas the school sample averaged 0.86 ± 0.17 visits. This suggests that children in the current study may have more severe asthma and thus use

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emergency health care resources more frequently than the general community population of low income children with asthma.

There were 77 children (28%) in the study population who had missing data for 1 or more of the 3 variables in the final regression model; 8 additional children were eliminated from the analysis because they themselves were smokers. The results are reported for the remaining 191 children. We compared the children with missing data with those with complete data to explore the possibility of bias. The children with missing data made fewer ER visits (1.42 ± 0.30 versus 2.50 ± 0.24 ; $p < 0.01$), but did not differ from children with complete data with respect to passive smoking or frequency of symptom days. On sociodemographic indices, children with missing data were younger (6.6 ± 0.8 yr versus 9.9 ± 0.2 yr; $p < 0.01$), but did not differ from the others with respect to sex, ethnicity, or socioeconomic status. We have no evidence to suggest that the differences observed would create bias, i.e., a different relationship among the study variables in the 2 groups of children.

Variables

The data included in the analysis were drawn from several sources: separate baseline interviews with the child and with the child's parent or guardian, hospital records of emergency health care use in the year prior to the interview, and tests of pulmonary function. The ER visits and hospitalizations for asthma were counted by reviewing medical records of study children from the 4 participating hospitals. To examine the possibility that the study sample was making significant use of health services at hospitals not participating in the study, we reviewed Medicaid records of total health care use by the 88 families in the study who were receiving public assistance. Only 6 children (7%) made any ER visits and only 1 child (1%) was hospitalized in a nonparticipating hospital during the baseline year. We concluded that the hospital record review did not significantly underestimate ER use or hospitalizations for asthma.

Pulmonary function testing was conducted during a random clinic visit in the year after the baseline interview. A waterless wedge spirometer (Jones Medical Instrument Co.) was used to measure 3 factors: FEV₁, peak expiratory flow rate (PEFR), and mean forced expiratory flow during the middle half of the forced vital capacity (FEF₂₅₋₇₅). Each child repeated the measurement 3 times, and we used the highest values in the analyses. Data are reported both as raw scores and as a percentage of predicted normal values (32).

Passive smoking by the child was measured by asking the parent who was interviewed if he or she or anyone else in the house smoked. Passive smoking was given a score of zero if no one in the house smoked, and a score of 1 if the respondent or someone else in the house smoked. Data to measure the child's dose of passive smoking was not collected, nor was paternal or maternal smoking assessed. To control for active smoking we asked

children, after guaranteeing confidentiality, if they ever smoked cigarettes, and the 8 children who said they did were removed from the analysis.

We did not obtain data on the presence or use of gas stoves. According to estimates by the public utility serving New York City, however, more than 99% of the families in our referral area use gas stoves. Therefore, it is unlikely that variations in nitrogen dioxide exposure because of the presence or use of gas stoves affected the frequency of ER visits.

Statistical Analysis

We used multiple regression techniques to test the hypothesis that passive smoking was associated with the frequency of ER visits and acute hospitalizations for asthma and with decreased levels of pulmonary function. A second goal of the statistical analysis was to discover whether any additional variables were significantly associated with health care use or with pulmonary function. A split sample procedure was used to evaluate the reliability of the ER visit model. The entire study population was randomly divided into 2 halves. Using the first half of the sample, we developed a regression model that fit the data best by minimizing the estimated standard deviation of regression. In addition to passive smoking, 34 other variables (see *Appendix 1*) were entered into the regression model using a backward elimination procedure. Because the number of variables was large in relation to the number of cases, the variables were entered sequentially in groups of 10 or less. The strongest predictors were retained and the weaker variables were eliminated until all the variables had been included in the regression and the best fitting model obtained.

The reliability of this model was evaluated by applying it to the data from the second half of the sample. We looked for consistency in the magnitude and direction of the regression coefficients across the 2 samples. The variables included in the final model had this consistency. Final values for the regression coefficients were obtained by applying the model to the full study sample. The association of specific variables with frequency of health care utilization was evaluated by the statistical significance of their regression coefficients in the final model using the full study sample. Statistical significance was defined as $p < 0.05$ using a two-tailed test.

There were 5 pairs of siblings among the 191 children who had complete data for the variables in the regression model; these siblings shared a common environment with respect to passive smoking and other variables. We assumed, however, that the emergency health care use and pulmonary function levels of siblings were statistically independent given the variables controlled in the model.

Because the distribution of ER visits was skewed toward the upper tail, we applied the square root transformation ($y = \sqrt{x}$) to approximately normalize the distribution. The regression analysis was conducted using the transformed scores. When final regression

models using transformed and untransformed ER visits were compared, there was no significant difference in the coefficients of the predictor variables or in the distribution of the residuals, so for simplicity the findings are presented using untransformed scores.

After the findings from the final regression model were obtained, we examined the distributions of the predictor variables and the residuals from the model. Observation of ER visit frequency plotted against frequency of days with asthma symptoms per month indicated that the relationship between these variables was curvilinear. To adjust for this, we performed a logarithmic transformation of the symptom days score ($x' = \log [1 + x]$) and found that the transformation improved the fit of the linear regression model to the data. We also tested for interaction between passive smoking and the frequency of symptom days, but no interaction was found.

Upon examination of the residual score (observed ER visits minus predicted ER visits) from the normal regression model, we note that 9 cases (5%) were in a skewed upper tail of the distribution, more than 2 standard deviations above the mean. Because the normal regression model assumes normally distributed errors, we explored other regression models that allow skewed count data distributions in order to assess the validity of the observed significance levels of the coefficients for passive smoking and days with asthma symptoms in the normal regression model. A geometric regression model was fitted to the data by maximal likelihood estimation and the results confirmed the significance of the coefficients (33, 34).

We also conducted a path analysis (35, 36) to explore causal relationships among the variables associated with ER visits. Path analysis is an interpretation of the relationships between the variables based on 2 assumptions: (1) that a weak causal order among the variables is known, and (2) that the relationships among the variables are causally closed. A weak causal order means that although X may or may not affect Y, Y cannot affect X. Causal closure means that X and Y are causally close to systematic outside influence with respect to their covariation. The path coefficients are standardized regression coefficients obtained by regressing each variable in the model on all the variables that are assumed to cause it. The logarithmic transformation of data with asthma symptoms was used in the path analysis.

Results

Emergency Room Visits

Children in the study sample made an average of 2.50 ± 0.24 ER visits per year. The ER visits ranged from zero to 20 but 75% of the sample made 3 or less visits per year. The results of the regression analysis are presented in table 1. Only 2 variables, passive smoking and the frequency of days with asthma symptoms per month, were significantly associated

TABLE 1
REGRESSION COEFFICIENTS OF VARIABLES ASSOCIATED WITH ER VISITS*

Variable	b	SE	Beta	p Value
Passive smoking (x_1)	1.34 (b_1)	0.50	0.19	0.008
Days with asthma symptoms per month (x_2)	0.53 (b_2)	0.22	0.17	0.02
Constant	0.91 (a)	0.53		0.08

* $n = 191$; $R^2 = 0.08$; standard deviation of regression = 3.46, $F = 6.11$, $df = 2,188$; $p = 0.003$. The regression model is $y = a + b_1x_1 + b_2x_2$, where y = number of ER visits; x_1 = passive smoking (1 if smokers present, 0 if smokers absent); b_1 = regression coefficient for x_1 ; x_2 = frequency of asthma symptom days per month; b_2 = regression coefficient for x_2 ; a = constant.

associated with ER visits. The variable most strongly associated with ER visits was the presence of smokers in the household. Fifty-three percent of the adult respondents indicated that they or another household member smoked. The mean frequency of annual ER visits observed for children from smoking households was 3.09 ± 0.40 , and the mean for children from nonsmoking households was 1.83 ± 0.29 . Using the regression equation shown in table 1, the predicted annual frequency of ER visits, for the mean frequency of asthma symptoms (8.86 ± 0.76 days per month), was 3.46 ER visits for children exposed to passive smoking, but only 2.12 for children who were not exposed. The predicted increase in annual ER visits attributable to passive smoking was 1.34 ± 0.50 visits (table 1), an increase of 63%. The distribution of annual ER visits by children exposed to passive smoking is compared in figure 1 with the distribution of ER visits by children from households without smokers. The histogram shows the positive association between passive smoking and ER visits.

We explored the effect of recoding the smoking variable to reflect the presence of 2 or more smokers in the household.

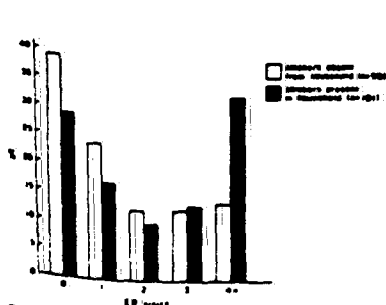


Fig. 1. Distribution of annual ER visits by presence or absence of smokers in the household. The 5 light bars sum to 100% of the children from nonsmoking households. The 5 black bars sum to 100% of the children from households with smokers. Note that 39% of the children with smokers absent made no ER visits compared with 29% of children with smokers present. In contrast, only 13% of children with smokers absent made 4+ ER visits compared with 32% of children with smokers present.

There were 20 households with 2 or more smokers: children from these families averaged 3.15 ± 0.90 ER visits per year compared with 3.07 ± 0.45 ER visits for children from households with only 1 smoker. The difference between these observed frequencies was not significant, and inclusion of this category of more intensive passive smoking exposure did not improve the fit of the regression model.

We were not able to assess directly the independent effects of mothers' and fathers' smoking behavior. Eighty-seven percent of the respondents, however, were either the child's mother or a female relative who had assumed the role of the child's principal caretaker. Because the father was often not present in the home, we reasoned that a comparison of smoking by the principal caretaker and by other people in the household would be an appropriate substitute for maternal and paternal smoking in this population. We eliminated the 24 cases in which the respondent was a male or was not the child's everyday caretaker, and compared the frequency of the child's ER visits in 3 groups: households in which the principal caretaker was the only smoker,

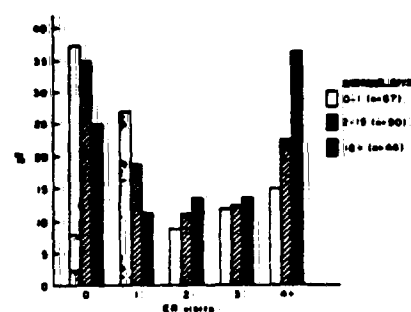


Fig. 2. Distribution of annual ER visits by frequency of asthma symptom days per month. Light bars sum to 100% of children with 0 to 1 symptom days, striped bars sum to 100% of children with 2 to 15 symptom days, and black bars sum to 100% with 16+ symptom days per month. Note that 37% of children with 0 to 1 symptom days made no ER visits compared with 25% of children with 16+ symptom days. In contrast, only 15% of children with 0 to 1 symptom days made 4+ ER visits compared with 36% of children with 16+ symptom days.

households where only other people smoked, and households where both the caretaker and another person smoked. No significant difference was observed among the 3 categories of smoking exposure.

Children in the study sample had an average of 8.86 ± 0.76 days with asthma symptoms per month. The frequency of symptom days per month was also significantly associated with ER visits (table 1). This association was curvilinear: as symptom days increased, the corresponding increases in ER visits grew smaller. Children with low frequency (zero to 1 day) averaged 1.73 ± 0.33 visits; with moderate frequency (2 to 15 days), 2.65 ± 0.43 visits; with high frequency (16 to 31 days), 3.39 ± 0.60 visits. The distributions of annual ER visits by children with low, moderate, and high frequency of symptom days are shown in figure 2. The histogram shows the positive association between frequency of wheezing days and ER visits.

Because passive smoking has been associated with increases in the occurrence of symptoms of asthma (12, 13, 18), we reasoned that there could be 2 ways in which passive smoking affects ER visits. The first is a direct effect of smoking on ER visits. The second is an indirect effect in which passive smoking increases the frequency of days with asthma symptoms, which in turn increases ER visits. To evaluate these effects, we estimated a simple path model in which we assumed that passive smoking was an exogenous variable that had both a direct effect on ER visits and an indirect effect on ER visits through frequency of days with asthma symptoms. A path analysis of the effects of the variables in this model is presented in figure 3. The results show that the effect of smoking on ER visits is almost entirely direct, with a path coefficient of 0.19. Passive smoking has

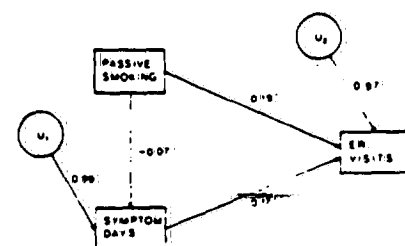


Fig. 3. A path model of the effects of passive smoking and frequency of asthma symptoms on ER visits. The path coefficients show the magnitude of the assumed causal effects indicated by the arrows. U_1 is the error term representing the unexplained variation in frequency of days with asthma symptoms; U_2 is the error term for ER visits; asterisk indicates $p < 0.05$.

no significant effect on the frequency of days with asthma symptoms (-0.07) and no indirect effect through symptom days on ER visits ($-0.07 \times 0.17 = -0.01$).

To rule out the possibility that the association of passive smoking with ER visits was due to some other variable, we conducted a regression analysis to identify any variables that might cause both increased smoking by family members and increased ER visits by the child with asthma. We found two—ethnicity and employment status—that had significant associations with smoking, but both variables had nonsignificant, inverse relationships with ER visits. Black families had more smokers than did Hispanic families, but made fewer ER visits. Families with 1 or more members employed full time had more smokers than did families without a wage earner, but also made fewer ER visits. Thus, neither variable had a significant effect on the relationship between passive smoking and ER visits.

To explore the possibility that non-smoking parents were more health conscious and followed more careful preventive measures that resulted in fewer ER visits, we examined a subindex of preventive measures drawn from the index of family asthma self-management activities (23), but found no associations with passive smoking or with ER visits.

Hospitalizations

Seventeen percent of the children in the study sample had been hospitalized during the year prior to enrollment in the study; the mean number of hospitalizations was 0.20 ± 0.04 . Passive smoking was not significantly associated with annual frequency of hospitalization. Only 2 variables, the number of the child's siblings with asthma (regression coefficient, 0.16 ; $p < 0.05$) and the frequency of missed outpatient clinic appointments (regression coefficient, -0.21 ; $p < 0.01$), were significantly associated with hospitalizations.

Pulmonary Function

The mean value for %FEV₁ in the study sample was $72 \pm 2\%$. The mean pulmonary function scores presented in table 2 indicate that passive smoking did not have a significant effect on any of the 3 indicators of pulmonary function studied. A regression of %FEV₁ on the variables measuring sociodemographic status, disease characteristics, allergens and irritants in the home, and familial history of asthma indicated that none of

TABLE 2
MEAN PULMONARY FUNCTION SCORES BY PRESENCE OR ABSENCE OF SMOKERS

Test*	Smokers in Household		p Value†
	Absent (n = 59)	Present (n = 60)	
FEV ₁ , L	1.49 ± 0.08	1.80 ± 0.08	NS
%FEV ₁	72.05 ± 2.38	71.71 ± 1.92	NS
PEFR, L/s	2.74 ± 0.19	3.19 ± 0.18	NS
%PEFR	74.03 ± 3.56	78.67 ± 2.95	NS
FEF ₂₅₋₇₅ , L/s	1.42 ± 0.10	1.60 ± 0.10	NS
%FEF ₂₅₋₇₅	58.67 ± 3.68	61.22 ± 3.59	NS

* For each test the first line reports the mean \pm SEM of the raw scores and the second line reports the raw scores as a percentage of predicted normal values (32).

† One-way analysis of variance.

these factors was significantly associated with %FEV₁.

Health Care Costs

To assess the impact of passive smoking on health care costs for children with asthma, we estimated the cost of an ER visit to the participating hospitals during the study period. The average cost of an ER visit, including medications, was 69 dollars. Multiplying this cost by the number of additional ER visits attributable to smoking (1.34 ± 0.50 with 95% confidence interval from 0.36 to 2.32), the estimated additional health care cost for emergency care for asthma was 92 ± 68 dollars per year (95% confidence interval from 24 to 160 dollars) for families with 1 or more smokers in this low income, urban, minority population.

Discussion

The association between smoking in the child's home and the frequency of ER visits is based on parents' reports of smoking behavior and should be interpreted with some caution. No objective evidence of smoking behavior by household members was collected, nor was any attempt made to demonstrate that children had significant levels of exposure to tobacco smoke. The proportion of respondents in the study sample who said they smoked (34%) is identical to the proportion of smokers among females between 21 and 44 yr of age reported in a recent nationwide survey (37). If, in fact, some respondents who did smoke concealed this information, the effect would be to diminish the observed association between smoking and ER visits.

The association between passive smoking and ER visits is a strong one. The presence of even 1 smoker in the household increased the annual frequency of

the child's ER visits by 63%. The frequency of days with asthma symptoms per month was also significantly associated with ER visits. There was, however, no relationship between passive smoking and the frequency of days with asthma symptoms. This finding is puzzling because one mechanism by which passive smoking can increase ER visits is by increasing the frequency of symptoms, and it raises the question of how passive smoking affects ER visit frequency.

One possibility is that there are measurement errors in parents' perception of the child's symptoms. Low level asthma symptoms may be difficult to notice, or like other common symptoms, may simply be taken for granted and thus under reported. An alternative possibility is suggested by the well-established finding that people with asthma can have air-flow obstruction without experiencing symptoms of breathlessness, and that at any given level of obstruction, reports of breathlessness vary considerably (38–40). Children themselves may not notice or report symptoms to their parents, thus obscuring the association between passive smoking and chronic symptom frequency. Furthermore, in a study of adults with asthma, Burdon and coworkers (40) found that patients with increases in baseline air-flow obstruction—a characteristic of our sample with mean %FEV₁ equal to 72%—were less able than patients with normal baseline air flow to detect breathlessness in response to a histamine challenge.

Recent findings that link passive smoking, histamine reactivity, and reduced perception of breathlessness, however, suggest a more complete explanation for the association of passive smoking with ER visits without a corresponding increase in chronic symptoms. First, Knight

and Breslin (18) found that experimentally controlled passive smoking increased sensitivity to histamine challenge in patients with asthma after a 4-h period, well after pulmonary function returned to normal. They suggest that passive smoking sensitizes the airways to react more strongly to other sources of irritation and thus potentiates acute episodes that would not otherwise have occurred. Second, Burdon and coworkers (40) observed that subjects with asthma who were more responsive to histamine challenge were less able to detect breathlessness. A logical extension of these two findings is that chronic passive smoking may reduce the ability to detect breathlessness by increasing airway sensitivity to histamine. Thus, in the absence of other asthma triggers that start an acute episode, the frequency of reported symptoms may decrease among children chronically exposed to tobacco smoke. We speculate that if another trigger does provoke an acute episode, the reduction in ability to recognize breathlessness is likely to result in delayed treatment, thus adding to the severity of the episode and the likelihood of eventually requiring emergency medical treatment. These 2 effects may thus account for both an increase in acute episodes leading to ER visits and a lack of observable change in chronic symptoms.

Although passive smoking was associated with ER visits, it was not associated with impairment of pulmonary function. This finding is not inconsistent with the mechanism proposed above because increased reactivity to histamine challenge is often present in patients with normal baseline pulmonary function (41). The lack of association between passive smoking and hospitalizations, however, does raise questions about the proposed histamine reactivity mechanism because heightened airway reactivity and reduced awareness of breathlessness would result in more severe episodes that receive delayed treatment; this in turn would be expected to result in increased hospitalizations.

This study provides evidence that passive smoking by children living in households with 1 or more smokers is significantly associated with increased use of emergency health care services. Health care providers can help prevent ER visits among children with asthma, and thus reduce health care costs, by explaining the association between smoking and ER visits to family members, encouraging them not to smoke, and referring them

to smoking cessation programs. Although we have no direct evidence that passive smoking heightened airway reactivity or reduced recognition of breathlessness in our study sample, such changes, if present, would provide a plausible explanation for our findings. We think that research to explore these possibilities is worthwhile.

Appendix 1

Additional variables included in the analysis:

- I. An index of allergens and irritants in the home.
- II. Parents' report of the child's average monthly frequency of days with symptoms of asthma.
- III. Family management practices:
 - Frequency of problems adhering to medication schedule.
 - Frequency of missed clinic appointments.
 - An index of self-management activities used to control asthma.
 - An index of criteria for deciding if medical help is needed to manage asthma symptoms.
 - Parents' level of confidence in ability to manage asthma.
- IV. Coverage of child by Medicaid.
- V. Nonemergency care:
 - Parents' rating of acceptability of outpatient clinic waiting time.
 - Parents' satisfaction with amount of information about asthma provided by outpatient clinic physician.
 - Continuity of care in clinic.
 - Frequency of parents' questions to physician.
- VI. Sociodemographic variables:
 - Sex of child.
 - Age of child.
 - Age of parent/guardian.
 - Ethnicity/race.
 - Employed person in household.
 - Mother's employment status.
 - Mother's years of education.
 - Mother's marital status.
 - Number of people in household.
 - Number of people per room.
 - Telephone in household.
 - Change of residence in last five years.
- VII. Health beliefs:
 - Health locus of control scale.
 - Effectiveness of medicine in preventing attacks.
 - Seriousness of child's asthma.
 - Belief that mild attacks require hospital or clinic visit.
 - Belief that asthma is more frightening than other diseases.
 - Belief that asthma can lead to other health problems.
- VIII. Social support:
 - Number of adults in household who help care for child's asthma.
- IX. Stress during asthma attacks:
 - Parental fear child might die during most recent attack.
- X. Family history of asthma:
 - Parental history of asthma.
 - Siblings with asthma currently.

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Toyoshima, K., Hayashida, M., Yasunami, J., Takamatsu, I, Niwa, H., Muraoka, T. "Factors influencing the prognosis of wheezy infants" J Asthma 24(5): 267-270, 1987.

ABSTRACT. Forty-eight wheezy infants were followed up for 25 to 44 months. These infants were classified into three groups: those with asthma (developed asthma later), the wheezy group (had successive wheezing episodes), and the non-wheezy group (grew out of the wheezy episodes).

Serum IgE levels at the first visit were not significantly different in the three groups, but the frequency of exposure to cigarette smoke was higher in the asthma and wheezy groups than in the nonwheezy group.

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Factors Influencing the Prognosis of Wheezy Infants

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ABSTRACT

Forty-eight wheezy infants were followed up for 25 to 44 months. These infants were classified into three groups: those with asthma (developed asthma later), the wheezy group (had successive wheezing episodes), and the nonwheezy group (grew out of the wheezy episodes).

Serum IgE levels at the first visit were not significantly different in the three groups, but the frequency of exposure to cigarette smoke was higher in the asthma and wheezy groups than in the nonwheezy group.

INTRODUCTION

Most wheezy infants grow out of wheezing episodes in childhood. But some wheezy infants will have recurrent wheezing attacks in childhood or become asthmatics.

It is important for clinicians to anticipate the prognosis of the wheezy infants, if possible. We followed up the wheezy infants for

a couple of years, and we were aware of the fact that passive smoking worsens the prognosis of wheezy infants.

MATERIALS AND METHODS

We selected 65 nonfebrile wheezy infants less than 3 years old who had no dyspnea

typical of asthma. The questionnaire (Figure 1) was filled out by the doctors during the interview with the mothers. At the first visit, venous blood was drawn for hematology and determination of serum IgE. The state of wheezing was reevaluated 25 to 44 months later by examining the medical chart or by telephoning the mothers. Reliable information was obtained in 48 cases (33 boys, 15 girls).

Serum IgE levels were assayed by the ELISA method with the Phadezyme Kit (Pharmacia). Serum IgE levels were compared with the old matched mean value for healthy infants by Furukawa et al. (1), and the level was judged as high when the level

was a standard deviation higher than the mean value, and extremely high when the level was two standard deviations higher than the mean value.

The infants who had more than 5% peripheral blood eosinophils were diagnosed as eosinophilic.

Comparability of the groups was evaluated by the chi square test, Fischer's exact test, or Student's *t* test.

RESULTS

The mean age at the first visit was 14.9 ± 8.6 months (mean \pm SD). The infants were

Name _____	Sex M. F.	Birthday _____
Date _____	Age _____	
IgE (ELISA): _____	IU/ml	
Hematology WBC: _____	Eo: _____	%
1. Major allergy in relatives: + -		(Atopic dermatitis Asthma, rhinitis Recurrent urticaria)
2. Minor allergy in relatives: + -		(Urticaria Adverse drug reaction)
3. Past history of wheezing: + -	Initial age: _____	Season: _____
4. Allergic past history Eczema: + -, Allergic rhinitis: + -, Recurrent urticaria: + -		
5. Past history of food allergy: + -		
6. Fever with wheezing: + -		
7. Birth weight: _____ g		
8. Disturbances at birth: + - (_____)		
9. Start of formula milk: _____ month(s)		
10. Start of fruit juice: _____ months		
11. Feeding method: breast formula		
12. Vaccination history:		
13. Symptoms at first visit: Wheezing (+ -), Fever (+ -)		
14. Smoking habits in family: Father (++ + -), Mother (++ + -), Others (++ + -)		

Figure 1. Questionnaire completed in interviews with the mothers of the wheezy infants.

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classified into three groups: The first (the asthma group) included 12 wheezy infants who were diagnosed later as asthmatic. The second group (wheezy) comprised nine wheezy infants who still had wheezing episodes in the last year of the observation period. The third group (nonwheezy) included 27 infants who had no wheezing episodes in the last year of the observation period. The infants' mean age did not differ significantly between the groups (Table 1).

The findings in each group are summarized in Table 2. The statistical differences between the groups were calculated. Hyperglobulinemia E levels, family history of allergy, history of wheezing and of allergic diseases, disturbances at birth, breast feeding, and fever

episodes with wheezing were not different statistically between the groups. Eosinophilia was more frequent in the asthma group than in the other groups. Infants in the asthma and wheezy groups lived with family members who smoked heavily. The mean age when the initial wheezing episode occurred was greater in the asthma group than in the other groups.

DISCUSSION

Some investigators have reported that IgE levels in cord blood or in infants predict the development of atopic diseases in later life (2-4). Our findings show that IgE levels in wheezy infants do not predict the development of asthma or continuation of wheezing episodes. On the other hand, eosinophilia was more frequent in the asthma group than in the other groups. Considering these two findings, asthma may develop through a non-IgE-mediated allergic process. But this cannot be concluded only by our findings.

Table 1. Mean Age of Each Group

GROUP	INFANTS	MEAN AGE (mo)
Asthma	12	18.3 ± 9.4
Wheezy	9	14.0 ± 7.1
Nonwheezy	27	13.7 ± 8.5

Table 2. Clinical Features of Each Group

	HIGH IgE	EXTREMELY HIGH IgE	EOSINOPHILIA	FAMILY HISTORY	HISTORY OF WHEEZING	HISTORY OF ALLERGIC DISEASES
1. Asthma group	5/11	1/11	6/11	8/12	9/12	7/12
2. Wheezy group	4/8	2/8	0/7	6/9	8/9	4/9
3. Nonwheezy group	6/26	4/26	2/24	12/27	20/27	10/27
Differences (1 + 2/3 1/2 1/3	NS	NS	p = 0.05 p = 0.025 p = 0.006	NS	NS	NS

	DISTURBANCE AT BIRTH	FORMULA MILK < 1 mo OLD	SMOKING IN FAMILY	FEVER WITH WHEEZING	AGE OF INITIAL WHEEZING (mo)
1. Asthma group	1/12	6/11	9/10	2/11	14.5 ± 8.7
2. Wheezy group	2/9	3/9	8/8	1/9	9.0 ± 6.0
3. Nonwheezy group	3/27	13/26	13/22	5/26	8.1 ± 8.1
Differences (1 + 2/3 1/2 1/3	NS	NS	p = 0.01	NS	p < 0.1 p < 0.05

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The fact that parental smoking affects childhood airway diseases has been reported by others (5,6). But it is not clear whether parental smoking increases the morbidity of infantile asthma. Our findings showed that the infants in smokers' families had successive wheezing episodes or developed asthma more frequently. Accordingly, we can conclude that passive smoking inhibits the outgrowing of wheezing in infants. We could not identify the mechanism by which passive smoking affected the infantile airways, but we should advise the families whose infants have wheezing episodes to stop smoking.

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Kershaw, C.R. "Passive smoking, potential atopy and asthma in the first five years" Journal of the Royal Society of Medicine 80: 683-688, 1987.

SUMMARY: Evidence of prolonged exposure to cigarette smoke was sought in a group of 86 children aged five years and under with moderately severe asthma, and in 1199 infants from a mixed background population of Armed Service and civilian families. Asthmatics with a normal serum IgE (less than + 1s.d. for age) made up almost half of the cases, and, compared with those with an elevated serum IgE (+ 1s.d. for age or more), a greater proportion were male, had experienced prolonged exposure to cigarette smoke, were from Service families and already had fixed chest deformity. It is suggested that, in addition to facilitating the expression of asthma in young potential atopics, passive smoking may be an important contributory cause of the more severe disease reported in the so-called 'intrinsic' group. Perhaps the burden of illness and the extent of exposure noted in this survey will prompt renewed efforts to be made to discourage smoking in families, particularly two years before and for at least five years after the birth of a child.

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Passive smoking, potential atopy and asthma in the first five years

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Keywords: asthma, passive smoking, armed services, atopy, chest deformity

Summary

Evidence of prolonged exposure to cigarette smoke was sought in a group of 86 children aged five years and under with moderately severe asthma, and in 1199 infants from a mixed background population of Armed Service and civilian families. Asthmatics with a normal serum IgE (less than +1 s.d. for age) made up almost half of the cases and, compared with those with an elevated serum IgE (+1 s.d. for age or more), a greater proportion were male, had experienced prolonged exposure to cigarette smoke, were from Service families and already had fixed chest deformity. It is suggested that, in addition to facilitating the expression of asthma in young potential atopics, passive smoking may be an important contributory cause of the more severe disease reported in the so-called 'intrinsic' group. Perhaps the burden of illness and the extent of exposure noted in this survey will prompt renewed efforts to be made to discourage smoking in families, particularly two years before and for at least five years after the birth of a child.

Introduction

Passive parental smoking has been shown to be linked to respiratory infections, impaired lung development and bronchial lability during vulnerable periods in a child's growth and acquisition of immunity¹⁻⁴. Despite the fact that passive smoking could well be the most important 'non-communicable' environmental factor involved in the aetiology of early asthma, only recently does it appear that a detailed account of this aspect of the child's early environment has been considered in prospective surveys of asthma following lower respiratory tract infections^{5,6}. Even now, the extent to which passive smoking affects the severity and natural history of either atopic or non-atopic (perennial or 'intrinsic') asthma in small children is unclear.

Although the prevalence of parental smoking has shown a gradual decline in the past decade, the rate of fall is sex and social class related and there is evidence that the overall percentage of smokers and of smoking parents in South East Hampshire has generally been higher than in England and Wales as a whole⁷. There is also some evidence that parents of asthmatic children at age 15 years smoke less than the general population⁸. However, both at the Royal Naval Hospital, Haslar, and in the local community, the opposite was observed, i.e. the parents of very young children with a variety of obstructive airways diseases were often active smokers.

The aim of the present survey was therefore to define a population of young, more severe asthmatics and compare smoking behaviour in their parents with that of the general background population of parents locally in the Portsmouth area. At the same time, a more detailed assessment of atopic

potential, immunization status, and chest deformity was undertaken in the asthmatic children.

Methods

Data on the background population were obtained by Gosport health visitors who enquired about regular smoking in both parents and other resident members of the household at the four-week examination for all children born in Gosport from April 1983 to March 1984 inclusive. This information was routinely collected as part of a multi-centre risk-related sudden infant death syndrome intervention study. An active smoker was defined as one who regularly smoked more than 5 cigarettes a day. A similar format of enquiry was used to ascertain those who had been resident in the household of asthmatic children and who had been active smokers for more than 50% of the child's first three years of life. An asthmatic was defined as any child under the age of six who had had three or more bouts of bronchitis or bronchiolitis (persisting cough and/or wheeze with illness lasting for 48 hours or more) in any six-month period and who in addition had had either definite intermittent wheeze or chronic night cough. This definition was used prospectively to screen all children referred to hospital with respiratory illness between April 1983 and January 1985, and the group thus comprised a consecutive series of young children with moderately severe asthma.

At the time of enrolment a careful enquiry was made by the author of family history of atopic symptoms in first-degree relatives, the number of previous admissions to hospital for chest problems and pertussis immunization status. An assessment was made of any chest deformity. Unless there was already clear and reproducible evidence of associated allergic eczema or urticaria, blood was taken for estimation of serum IgE and IgE antibodies to house-dust mite, grass, tree and weed pollens, and cat and dog (epithelium). Convalescent venous samples were taken when no oral steroid medication had recently been prescribed.

Atopic potential was thus assessed in three separate ways: in terms of the presence or absence of (1) a personal history of allergic eczema or urticaria; (2) a first-degree family history of atopic conditions; and according to (3) the level of a single convalescent estimation of serum IgE. Children regarded as having potentially non-atopic or 'intrinsic' asthma tended to show negative family histories, but, in particular, their serum IgE was less than 1 s.d. above the mean for age.

Results

In the 22-month period, 91 consecutively referred children aged under six years met the criteria for definition of asthma used for this survey. Comparison

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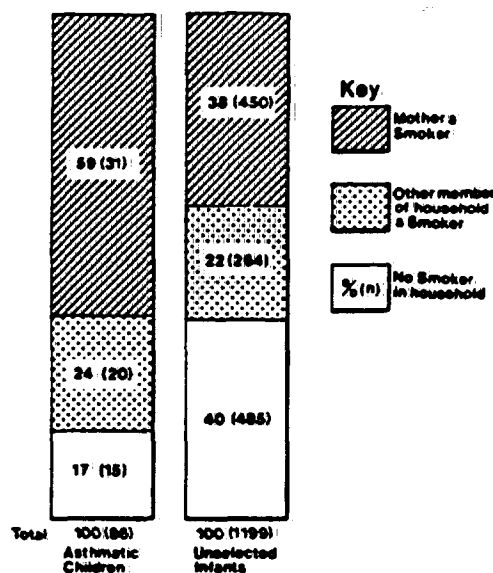


Figure 1. Prevalence of smoking in households of asthmatic children

with Ward diagnostic index and hospital statistics suggests that this group represented approximately one-quarter of all children seen with lower respiratory tract symptoms over the period and contained the majority of those with perennial and more severe illness. Five had persisting symptoms and signs and further investigations revealed specific diagnoses,

namely: cystic fibrosis (1M, 1F), tracheo-oesophageal fistula (1M), congenital collapsing left main bronchus with hypoplastic left lung (1M), immotile cilia syndrome (1M). The remaining 86 (57M, 29F) had asthma with a mean age at ascertainment of two years and seven months, by which time they had already had a mean of 2.15 admissions per child. In 9 of these children the presence of atopic eczema, a positive family history of atopy in first-degree relatives, and reproducible allergic reactions or positive skin tests in the child strongly suggested atopy, and serum IgE measurement was not undertaken. This group was, however, included in the comparison of the prevalence of smoking in members of the household with that in the background population.

Prolonged exposure to cigarette smoke

The results of the comparison of prevalence of smoking in the household are shown in Figure 1. The prevalence of smoking was clearly higher in the households of asthmatic children than in the background population. When the differences in prevalence of smoking are broken down according to the father's occupation, as in Table 1, it is evident that the major difference between the Service and civilian populations lies in the greater proportion of members of households smoking in the 'Service' asthmatics' families (87% cf. 79%). Significance ($\chi^2_{(1)} = 11.0$, $P < 0.01$) for this group was the highest of the four sub-groups, all of which showed increased prevalence of smoking in the households of asthmatic children, compared to the background population.

Table 1. Prevalence of smoking in relation to father's occupation

	Armed Service	Civilian
Mother a smoker:		
Asthma	23 (59%)	28 (80%)
Unselected	221 (37%)	229 (38%)
	$\chi^2_{(1)} = 6.4$; $P < 0.06$	$\chi^2_{(1)} = 7.8$; $P < 0.01$
Member of household a smoker:		
Asthma	34 (87%)	37 (79%)
Unselected	360 (59%)	364 (60%)
	$\chi^2_{(1)} = 11.0$; $P < 0.01$	$\chi^2_{(1)} = 5.6$; $P < 0.05$

Percentages refer to proportion of all service or all civilian.

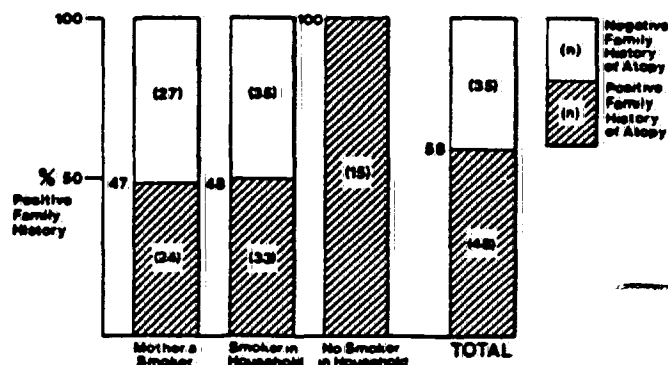


Figure 2. Smoking in households of asthmatic children in relation to family history of atopy

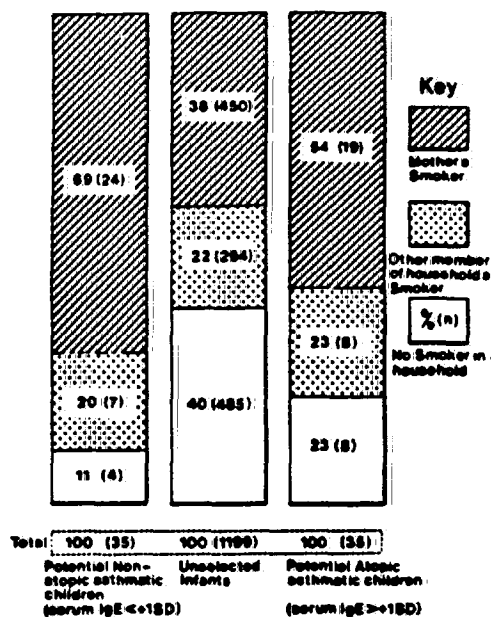


Figure 3. Prevalence of smoking in relation to atopic potential

Atopic potential

Family history: Information on family history of atopy in first-degree relatives was available in 83 of the 86 cases. From the data in Figure 2 it can be seen that in the absence of a positive family history, all the asthmatic children's households contained at least one member who was a regular smoker. All the non-smokers occurred in association with a positive family history of atopy, but even a personal or close family history of asthma did not appear to have discouraged smoking in the parents of many of these young asthmatic children.

Serum IgE: A single level of serum IgE was available for 70 of the 77 asthmatic children in whom atopic status was uncertain, but was unavailable in 7 either because they had moved from the area or defaulted the clinic.

Table 2. Pertussis immunization uptake for asthmatic children

	%	(n)
Potential non-atopic (serum IgE < +1 s.d.)	52	(27)
No smoker in family	50	(14)
Civilian family	46	(39)
Asthmatic children (all)	42	(69)
Member of household a smoker	39	(54)
Service family	37	(30)
Potential atopic (serum IgE > +1 s.d.)	35	(31)

The mean age of measurement of serum IgE in this survey was 2 years 11 months. On the basis of the single serum IgE measurement, 35 (50%) of the children tested were regarded as potentially atopic and an equal number potentially non-atopic. It can be seen from Figure 3 that a similar trend emerges, with the higher prevalence of active smoking occurring consistently in the households where the asthmatic child was potentially non-atopic. Differences between the potentially atopic and non-atopic households did not reach significance, but both of the groups with measured serum IgE showed significant differences when compared to the background population.

Pertussis immunization

For 69 of the 86 cases there was good recall of data on pertussis immunization status. The British Paediatric Association Immunization Committee's figures for pertussis vaccine uptake in the first three years of life (for 1982) are 53% for England and 59% for Wessex Region. Table 2 shows the comparison between the different sub-groups, with only 42% overall achieving positive status, i.e. in date with all scheduled immunizations. Thirty-three of this group of asthmatics (48%) had the double disadvantage of living in a household where there was an active smoker and being inadequately protected against pertussis.

Chest deformity

Seventy-one children were carefully examined by the author for evidence of fixed chest deformity, which in

Table 3. Chest deformity in asthmatic children

	With chest deformity Ratio (n)	Without chest deformity Ratio (n)	Trends in those with chest deformity
Family history of atopy			
Positive:negative	1.00:1 (30)	2.45:1 (36)	
Serum IgE			
Above +1 s.d.:below +1 s.d.	1.08:1 (25)	1.25:1 (36)	↓
Smoking in household			
Smoker:non-smoker	6.50:1 (30)	3.56:1 (41)	↑
Maternal smoking			
Smoker:non-smoker	2.00:1 (30)	0.95:1 (41)	
Pertussis immunisation uptake			
Immunised:non-immunised	0.57:1 (26)	0.64:1 (35)	↑
Occupation of father			
Armed Service:civilian	1.30:1 (30)	0.46:1 (41)	
Sex distribution			
Male:female	3.29:1 (30)	1.56:1 (41)	

most cases was manifest as a marked Harrison's sulcus and this was present in 30 (42%). More had developed chest deformity by the time of enrolment in the survey if they were male, came from Service families, had a negative family history of atopy, a serum IgE less than +1 s.d. (i.e. potentially non-atopic) and a mother or member of household who smoked (Table 3). Immunization against pertussis did not appear to confer protection against the development of chest deformity in this survey. These trends were not statistically significant. Overall a chest deformity was noted in 50% of those whose mothers smoked and 43% where a member of the household smoked.

Sex preponderance

Although there was a 66% male preponderance overall in the 86 cases (M:F 1.97:1), the preponderance in the group of potential non-atopic or 'intrinsic' asthmatics was 71% (25 of 35) compared to only 60% (21 of 35) in the potentially atopic; the male:female ratios were respectively 2.5:1 and 1.5:1. An increased male preponderance was seen also in asthmatics from Service families (2.8:1) and in those families where the mother smoked (2.1:1).

Discussion

Epidemiological studies of children with asthma and wheezy bronchitis have emphasized a high burden of illness, increasing prevalence and similar underlying mechanisms, with the need for a common approach to early diagnosis and management⁸⁻¹⁰. The recurrent ill health, multiple hospitalizations and early chest deformity seen in the young asthmatic children in this survey echo these findings. A most important variable, when comparing surveys of asthma, is difference in criteria used in definition¹¹. Below the age of six, an exact definition of asthma is difficult to apply. The one used in this survey has proved helpful in focusing on early diagnosis and optimal management in both general practice and district paediatric unit settings.

The probability that at least two populations of young 'wheezers' might exist has been considered for some time, but it has not been clear whether these were allergic and non-allergic, atopic and 'intrinsic', or bronchitic and asthmatic^{12,13}. The ventilatory response to exercise has been suggested as a good basis for separating such children. However, the poor reliability and reproducibility of bronchial lability testing in children under six years limits such a separation. Increased bronchial lability is considered to be a more likely explanation for the early male preponderance seen in young asthmatic children than atopic status which, in post-respiratory syncytial and other virus-induced wheezing, appears to be less important than it is in asthma in older children¹⁴. However, this explanation is not entirely convincing, and assessment of atopic status may have been inadequate in studies that have relied on family history alone¹².

Qualitative differences in the low levels of IgE at birth and in the first few years of life have permitted more accurate prediction of atopic respiratory disease, although in older children the relationship between single IgE levels and allergic symptoms remains controversial^{9,15}. In Sweden, where some of this work has been carried out, the prevalence

of asthma has been lower than in the UK and social conditions generally more favourable. It seems likely that some of the controversy which exists on the role of atopy has also arisen because variations in passive smoking and other important social factors have not been adequately taken into consideration in follow-up studies after virus, mycoplasma and bordetella infections, nor in bronchial lability studies on asthmatic children and their relatives^{12,16}. In the most favourable social circumstances, however, atopy may more clearly be shown to predispose to asthma occurring with or as a sequel to infection¹⁵⁻¹⁷.

The findings of the present Naval Hospital-based survey suggest that the majority (94%) of moderately severe young asthmatic children in whom atopic status is uncertain fall into one of three groups:

- (a) Serum IgE > +1 s.d. above mean for age and member of household a smoker for >50% of child's first three years (atopic, passive smoker).
 - (b) Serum IgE > +1 s.d. above mean and no smoker in household (atopic, non-smoker).
 - (c) Serum IgE within +1 s.d. of mean for age and member of household a smoker for >50% of the child's first three years ('intrinsic', passive smoker).
- A raised serum IgE and/or a mother who was an active smoker were noted in 84% of the 70 cases in whom IgE was measured.

It is particularly in the group of potentially non-atopic or 'intrinsic' asthmatics (Group C) that the major difference in male preponderance and parental smoking behaviour was observed. Exclusion of children with a personal history of eczema and a high local prevalence of smoking may have accounted for the high proportion of these 'intrinsic' cases (50% cf. 20% noted in other surveys)¹³. This separation into three groups may also help more satisfactorily to explain the early male preponderance in terms of the effects passive smoking might perhaps have in increasing bronchial lability and vulnerability to respiratory infections more in males than females.

The correlation of only 60.3% noted between raised serum IgE and positive family history of atopy in this survey might have been inferred from Kjellmann's findings¹⁸ that although a family history of atopy was present in 50% of his cases with a similar atopic disease, the total incidence of atopic disease was only increased from 15% to 25% in those with a positive family history. The predictive value of serum IgE contrasts with the poor specificity of family history in providing a useful index of atopic status. In the present study, 5 children showed positive RAST tests, but serum IgE in the normal range, suggesting that there may be a significant group of mild atopics unascertained. It has been suggested that the effect of parental smoking on serum IgE levels in young children is to make the rate of rise with age more rapid, and a significant difference has been shown at 36 months¹⁹. This would have had the opposite effect and made it more likely in the present study that atopic children would have been classified correctly.

Since the original survey undertaken by Colley *et al.*¹, there have been many others supporting their conclusions on passive smoking. The paper by Pullan *et al.*² in relation to respiratory syncytial virus infection is particularly clear in demonstrating the significance of maternal smoking, breast feeding, maternal care as assessed by the health visitor, and a single mother in relation to the severity of a young

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Figure 4. Paternal contribution - circa 1900. (Reproduced from *Pipe Dreams*, 1982; with kind permission of Pavilion Books)

child's respiratory illness. These findings are supported by the larger 'National Child Development' and 'Child Health and Education in the Seventies' studies in this country and numerous surveys from other parts of the world^{2,3,17,20-24}. More recently Webb *et al.*⁶, in a paper on continuing symptoms three and a half years after acute bronchiolitis, showed that of all the parameters (including family history of atopy and skin tests) considered, maternal smoking was the only one which, according to their data, reached significance at the 5% level. Other factors in addition to the development of the humoral response to house-dust mite and grass pollen antigens were inferred by Rowntree *et al.*²⁵ in their study on the continuing incidence of asthma at five years; and in a study on children at risk from atopic disease, Cogswell *et al.*²⁶ also noted that the one factor found to be associated with an increased prevalence of wheeze was the presence in the household of at least one parent who smoked.

Smoking behaviour may reflect a number of other social factors such as maternal stress. Medical care utilization is also closely bound up with parental smoking habit; nevertheless, a specific direct effect on aetiology of respiratory tract disease attributable to passive smoking seems likely. Some light may have been shed on the mechanism of this through the work of Tager *et al.*⁴. Acquired ciliary defects have been noted in nasal epithelia in children with respiratory infections, and it will be important to establish the frequency of similar defects in small children who experience significant passive smoking²⁷. Cotinine estimations have established the existence of tertiary smoking and been helpful in illustrating quantitatively in the child the chemical effects of passive parental smoking^{28,29}.

Previous studies in Gosport have demonstrated that maternal smoking and other child care disadvantages assessed by health visitors were relevant factors in the prediction of infants at risk from sudden infant death syndrome in both the local Service and civilian populations³⁰. The present survey illustrates that asthma and a family history of atopic disease are incorrectly regarded as contraindications to pertussis immunization. However, stress and adverse social factors are also suggested here and imaginative strategies will be required to counteract these³¹. The increased prevalence of parental smoking, poor uptake of pertussis immunization, and frequency of early chest deformity seen in Service families must be explained.

The evidence suggests that the unsolicited burden of passive smoking represents a significant health hazard to children (Figure 4). In addition to facilitating the expression of asthma in young potential atopics, it may be an important contributory cause of the more severe disease reported in so-called 'intrinsic' asthmatics³². Although health education programmes have not shown good immediate effect in general, a smoking cessation programme has been shown to be relatively effective in a group of sailors³³. There remains scope for further programmes, and a clear statement is required of the necessity to avoid smoking in households two years before and at least five years after the birth of a child.

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Murray, A.B., Morrison, B.J. "Passive Smoking and the Seasonal Difference of Severity of Asthma in Children" Chest 94: 701-708, 1988.

ABSTRACT. To learn whether asthmatic children are affected by passive smoking, we studied 240 unselected consecutively referred asthmatic subjects, aged 7 to 17 years. To discover whether children of smokers are affected more severely during the cold, wet season, when windows are closed and children are indoors, than during the warm, dry season, when houses are well ventilated and children spend more time outdoors, we compared lung function tests recorded during the two seasons. If seen during the cold, wet season, children of smoking mothers compared with those of nonsmoking mothers had a lower FEV1% (74 vs 86, $p=.00$), FEV25-75 percent (56 vs 75, $p=.00$) and PC20 histamine (0.85 vs 1.95, $p=.01$). There was a highly significant correlation between the number of cigarettes the mother smoked in the house and each of these lung function test results, indicating a dose-response relationship. Those seen during the warm, dry season, by contrast, did not have lower mean spirometric test results if their mothers were smokers than if nonsmokers, and there was no correlation between the number of cigarettes the mother smoked in the house and the result of any lung function test. Our results strongly support the hypothesis that cigarette smoke from the mother aggravates her child's asthma.

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Passive Smoking and the Seasonal Difference of Severity of Asthma in Children*

Andrew B. Murray, M.B.,† and Brenda J. Morrison, Ph.D.‡

To learn whether asthmatic children are affected by passive smoking, we studied 240 unselected consecutively referred asthmatic subjects, aged 7 to 17 years. To discover whether children of smokers are affected more severely during the cold, wet season, when windows are closed and children are indoors, than during the warm, dry season, when houses are well ventilated and children spend more time outdoors, we compared lung function tests recorded during the two seasons. If seen during the cold, wet season, children of smoking mothers compared with those of nonsmoking mothers had a lower FEV₁% (74 vs 86, $p = .00$), %FEF₂₅₋₇₅ percent (56 vs 73, $p = .00$) and PC₂₀ histamine

(0.85 vs 1.05, $p = .01$). There was a highly significant correlation between the number of cigarettes the mother smoked in the house and each of these lung function test results, indicating a dose-response relationship. Those seen during the warm, dry season, by contrast, did not have lower mean spirometric test results if their mothers were smokers than if nonsmokers, and there was no correlation between the number of cigarettes the mother smoked in the house and the result of any lung function test. Our results strongly support the hypothesis that cigarette smoke from the mother aggravates her child's asthma. (*Chest* 1988; 94:701-08)

Several studies have reported that children who are exposed to their parents' cigarette smoke are more likely than children of nonsmoking parents to wheeze and to have decreased spirometric test results.¹⁻⁴ Although this decrease in pulmonary function is thought to result from passive smoking, a causal relationship is not universally accepted. Doubt remains because some surveys find no difference in

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spirometric results between the children whose parents smoke and those whose parents do not smoke.^{1,9}

Weiss et al¹⁰ suggested a plausible explanation for the failure of these latter studies to show an association between parental smoking and impaired pulmonary function. It is that the surveys were conducted in Arizona, a place where the weather is warm and dry, where children spend more time outdoors, and where ventilation rates of houses are high. As a result, the amount of passive smoking may be less in smoking parents' children who live in Arizona than in those who live in a cold, wet area.

The indoor level of smoke appears to be low in Arizona, even when there is a smoker in the house. In a study carried out in Tucson, Lebowitz⁹ found that the indoor concentration of carbon monoxide (CO), an indicator of the smoke level, was comparable to the

outdoor concentration, even though a smoker was present. When a building is well ventilated, CO from cigarette smoke is rapidly removed, but when poorly ventilated, as is the case during the heating season in colder areas, the CO concentration increases.¹¹ The reason for reducing the ventilation rate in cold weather is to conserve energy.¹² The consequence is that in a heated building the air is recirculated and there is an accumulation of cigarette smoke, shown by high concentration of both CO¹³ and the mean mass respirable particulate (MRP), another indicator of the amount of cigarette smoke present.^{14,15} Dockery and Spengler¹⁶ found that smoke from one pack of cigarettes raised the MRP level by approximately 42 µg/cu m when the air in the building was being recirculated, but only by 18 µg/cu m when the air was not being recirculated.

If passive smoking is greater in cold, wet weather than in warm, dry weather, and if the smoke impairs lung function, we would expect children of smoking mothers in Vancouver to be more severely affected in the cold, wet season (October through May), than in the warm, dry season (June through September, Fig 1).¹⁶ During this warm period, windows and doors are left open, a practice that rapidly changes the indoor air.¹⁴

Asthmatic children are appropriate subjects for a study to find whether this seasonal difference is present, because their bronchi seem to be more sensitive to the effects of smoke than are those of normal children. The difference in spirometric test results between children of nonsmokers and smokers reported in asthmatic subjects¹⁷ is much greater than reported in representative groups of schoolchildren.¹⁸ In such a study the mothers' smoking habits are particularly important, since children have greater

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exposure to her smoke than to smoke from the father, judged by cotinine levels in the children's saliva. The level is significantly higher if the smoker in the family is the mother rather than the father.¹⁰

The present study had two purposes: (1) to confirm that asthmatic children of mothers who smoke do have lower lung function test results than those of mothers who do not smoke, and (2) to find whether these children of smokers are affected more severely in the cold, wet season than in the warm, dry season.

MATERIAL AND METHODS

Population

The series included every child with asthma or a wheezy chest who was aged 7 to 17 years and had been referred to one of us (ABN) at the Children's Hospital in Vancouver.

There were 847 subjects. Of these, 160 were being seen for the first time, and 67 had been examined on a previous occasion, they were being reassessed at the request of their primary care physicians. For both new and old patients only the data recorded at the initial visit during the period Nov. 1, 1983, to May 31, 1986, were used in the study.

Because of a long waiting list, an average period of four months elapsed between the date of referral and the day of the child's visit. As parents tend to forget instructions during such a long interval, every attempt was made to contact them by telephone 48 hours before the appointment. They were asked which medications the child was receiving and were instructed to discontinue those that might influence the bronchial challenge test.

Questionnaire

A trained interviewer put standardized questions to the patients and to the accompanying adult who, in 97 percent of cases, was a parent. All were asked how long the child had had the asthma or wheezing, whether the child had suffered from a cold or respiratory infection during the preceding two weeks, and whether the child had received recent medication—i.e., corticosteroid or antiasthmatic medication in the past 48 hours, theophylline in the previous 24 hours, or sodium cromoglycate or bronchodilator in the eight hours before the appointment.

Those who were being seen for the first time were also asked the following questions, whether a gas stove was used for cooking, the type of central heating in their house, whether they owned any furmed household pets, and whether either of the parents or any of the siblings had ever had asthma. These items of information had also been ascertained at a previous visit for those referred for reassessment, but because conditions could have changed since the original enquiry, these old data were not used in the present study. When the above questions had been completed, the parents or accompanying adults were asked how many cigarettes the mother and father smoked per day, both the total number and the number smoked while in the house.

The child was asked privately whether he or she smoked. Of the four who admitted to being smokers, two were children of a nonsmoking mother, and two were children of a smoking mother. Because the purpose of this study was to determine the effect of passive smoking only these four subjects were excluded.

Forced Expiratory Spirogram

Forced expiratory maneuvers were performed until there were three in which the forced vital capacity (FVC) agreed within 5 percent. This was achieved within five efforts on all except three children, all aged seven years, who were too uncoordinated or too

uncooperative to perform a forced expiratory maneuver. These children were eliminated from the series. In the remaining 840 subjects the tracing that had the greatest sum of FVC and forced expiratory volume at one second (FEV₁) was used for all measurements. The FEV₁ and the forced expiratory flow rate during the middle half of the FVC (FEF₂₅₋₇₅) were expressed as a percentage of predicted mean for age, sex, and height.¹¹

The spirogram was recorded with a Pulmonary (Jones Medical Instrument Co) waterless spirometer that was calibrated weekly with a known volume of carbon dioxide (CO₂) discharged at a standard velocity from a calibrator instrument.

The results of the tests were analyzed and printed by a Datamatic (Jones Medical Instrument Co) computer connected to the spirometer.

Bronchial Reactivity to Histamine

A bronchial challenge test was performed on all except the following subjects: those who had taken recent medication, as defined above; those who reported a cold or respiratory infection within the preceding two weeks; or those who had an FEV₁ less than 60 percent predicted, or was below 1 L in volume.

A modification¹² of the protocol of Cockcroft et al¹³ was used to find the threshold dose of histamine that would result in a fall of 20 percent in the FEV₁. After baseline spirometric measurements had been recorded the patient held a loosely fitting plastic mask to his face, inhaling an aerosol generated by air flowing at 5 L/min through a Wright nebulizer. The volume of solution nebulized was 0.2 mL/min. Doubling concentrations of histamine acid phosphate were given until the strongest concentration, 8 mg/mL, was reached. Children whose FEV₁ did not decrease by 20 percent when this concentration was administered were deemed, for the purpose of calculating the PC₂₀, to respond to double that concentration, i.e., 16 mg/mL histamine acid phosphate. There were 13 such subjects. The mothers of 12 of them were smokers, and the mother of the remaining one was a smoker.

Using a standard method,¹⁴ skin prick tests were performed on all subjects with the following materials: a negative (saline) and a positive (histamine) control solution, extracts of 1 percent Dermatophagoides farinae and 1 percent D. pteronyssinus (Bernard Division of Beecham Laboratories), dog and cat hair (Hollister), and alder, birch, and mixed grass pollens (Greer Lab).

The diameter of each resulting wheal was measured. If any wheal was 2 mm greater than that of the negative control solution, the test was considered positive.

The spirometric, bronchial challenge, and skin tests were performed by a technician who was unaware of the family's smoking habits.

Season

Spirometric and bronchial challenge test results in the children seen between June and September, the warm, dry season, were compared with those recorded between October and May, the cold, wet season in Vancouver¹⁵ (Fig. 1).

From October through May there are, on average, no degree days above 18°C. A "degree day" is defined as a measure of the departure for a day from some reference temperature. The reference temperature chosen for this study, (18°C) is the one used for residential space heating needs. Heat is required on the days when there is a negative departure from 18°C and no heat on the days when there is a positive departure. From early October until the end of May, therefore, windows and doors are closed every day to conserve heat.

Korngardt found that windows are left open for 30 hours a day in June and July but only for one hour a day in February and March. Under such circumstances the ventilation rate of the house is decreased, and the cigarette smoke generated in the house reaches high levels.^{16,17}

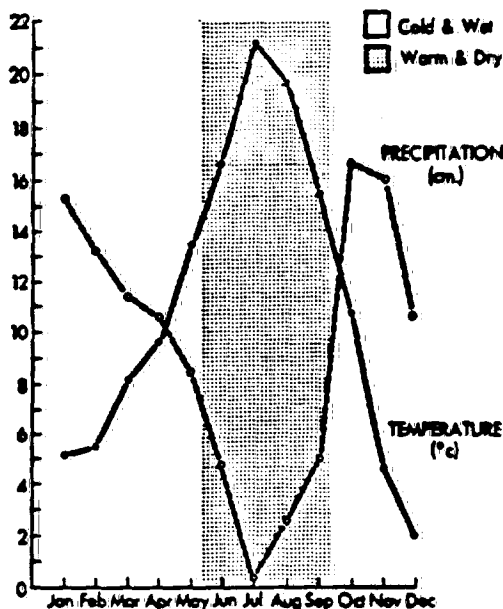


FIGURE 1. The mean monthly temperature and the mean monthly precipitation in Vancouver between November 1963 and June 1966.

From June through September there are degree days above 18°C in every month, and on these days ventilation is unrestricted, as air-conditioning is unnecessary for comfort. The mean maximum temperature in Vancouver in July and August is only 21°C.¹⁸ Of our patients in the Vancouver area, four had air-conditioning in the parents' bedroom, but none had air-conditioning for the whole house. Two patients from cities in the interior of the province had house-wide (central) air-conditioning, the family members in these houses were all nonsmokers.

Statistical Analysis

After elimination of the four children who were themselves smokers and the three who could or would not perform an acceptable spirogram, 240 subjects remained. 183 had mothers who were nonsmokers, 56 had mothers who were smokers, and the smoking status of one mother was unknown.

For statistical analysis, differences were tested by Student's *t* test for those variables on a continuous scale, or a scale approximating it, and by χ^2 for those which were frequencies. Pearson's product-moment and point biserial correlation coefficients, as appropriate, were calculated to assess association. A logarithmic transformation was applied to the number of cigarettes smoked by each of the parents, the PC_{25} , and to other variables that were skewed to the right. Multiple linear regression was carried out for each season separately.

RESULTS

The two groups of children were comparable for the following features: age, male-female ratio; the duration of asthma; the occurrence, during the preceding two weeks, of a respiratory infection, a condition that may have influenced lung function test results; the taking of recent medication; and the percentage with a positive skin prick test to an inhalant allergen, an indication of atopy (Table 1). The two groups did differ,

Table 1—Comparability of Groups

Features	Mother Nonsmoker (n = 183)	Mother Smoker (n = 56)	p Value (2-tailed)
All patients*			
Mean age, yr	11.0 ± 0.2	10.9 ± 0.4	0.84
Male:Female ratio	120:63	43:13	0.16
Duration of asthma*	6.7 ± 0.3	7.4 ± 0.5	0.26
Recent respiratory infection*	55 (34%)	20 (38%)	0.74
Recent medication*	50 (28%)	22 (41%)	0.12
Positive skin test	158 (86%)	46 (82%)	0.57
Size of mite reaction†	3.4 ± 0.3	1.7 ± 0.4	0.00
New patients*	n = 117	n = 37	
Family history of asthma*	39 (42%)	9 (30%)	0.34
Heating			
Hot air	73 (62%)	30 (54%)	0.48
Wood stove*	14 (12%)	6 (17%)	0.68
Gas for cooking*	7 (6%)	3 (8%)	0.96
Household pets	50 (43%)	22 (60%)	0.22

*When the informant did not know a particular item of information, the patient was omitted from the analysis for that item. The numbers omitted were as follows:

Mother's smoking status, 1; duration of asthma, 33; recent respiratory infection, 24; recent medication, 9; family history of asthma, 32; wood stove, 4; and gas for cooking, 3.

†The size of the mite reaction was not measured in 5. Mean ± SE are presented.

however, in the mean diameter of the wheal produced by a skin prick test with house dust mite extract. Children of nonsmokers had the larger reaction, indicating either that they had a potential for being more severely affected during the cold, wet season, the period when mite-sensitive subjects in Vancouver tend to have the worse asthma,¹⁹ or that they were more highly exposed to house dust mites,¹⁷ or both.

In the 155 patients who were visiting the Allergy Clinic for the first time and were asked the additional questions at that visit, the children of smoking and nonsmoking mothers were also comparable for the following variables: for the percentage of houses in which airborne allergens were circulated by a forced air heating system; the percentage exposed to emissions from gas stoves, used for cooking,²⁰ or from wood stoves, used for heating;²¹ ownership of pets to which they may have been allergic; and the proportion who had a parent or sibling with asthma (Table 1).

This newly seen group of 155 subjects were comparable in all respects to the group of 85 whose first visit to the clinic had been before the start of the study, except that the latter were older by a mean of two years and had had their asthma for one year longer (Table 2).

As in our previous study,¹⁷ there was a highly significant association between maternal smoking and indications of increased asthma severity in the patient. Children of smoking mothers had a lower mean $FEV_{1,25}$ and $FEF_{25-75\%}$, and had a lower mean PC_{25} histamine

Table 2—Comparability Between Old and New Subjects

Features	Old (n = 85)	New (n = 155)	p Value (2-tailed)
Mean age, yr	12.0 ± 0.3	10 ± 0.2	0.00
Male:Female ratio	56:27	106:49	1.00
Duration of asthma, yr*	7.6 ± 0.5	6.5 ± 0.3	0.06
Recent respiratory infection*	32 (40%)	43 (32%)	0.27
Recent medication*	31 (37%)	42 (29%)	0.24
Positive skin test	75 (88%)	130 (84%)	0.47
Size of mite reaction†	3.0 ± 0.3	3.1 ± 0.3	0.74
FEV ₁ %	83 ± 1.8	83 ± 1.4	0.91
FEF25-75%	66 ± 2.7	70 ± 2.3	0.47
PC ₂₀ histamine‡	1.49 ± 1.2	1.82 ± 1.2	0.52

*When the informant did not know a particular item of information the patient was omitted from the analysis for that item. The numbers omitted were as follows: duration of asthma, 33; recent respiratory infection, 24; recent medication, 9.

†The size of the mite reaction was not measured in five.

‡The PC₂₀ was performed on 104 subjects (geometric means are given). Mean ± SE are presented.

than did the children of nonsmoking mothers (Table 3).

There was also a significant correlation between the logarithm of the number of cigarettes the mother smoked while in the home and the FEV₁%, the FEF25-75%, and the logarithm of the PC₂₀ histamine, suggesting a dose response (Table 4).

Also, as reported in our previous study,¹² there was no association between the father being a smoker or a nonsmoker and the results of any of the above-mentioned tests (Table 3), nor did the number of cigarettes he was said to smoke at home correlate with any test results (Table 4). However, in the subgroup in which the father himself had verified the number of cigarettes he smoked while in the house, there was a correlation between the logarithm of this number and the logarithm of the PC₂₀ histamine ($r = -.60$, $n = 9$,

Table 3—Results of Lung Function Tests Classified by Smoking Habits of Parents

Feature	FEV ₁ %	FEF25-75%	PC ₂₀ † Geometric Mean
Mother*			
Nonsmoker (n = 183)	85 ± 1.2	73 ± 2.0	2.03 ± 1.1 (n = 78)
Smoker (n = 56)	76 ± 2.4	80 ± 3.4	0.91 ± 1.3 (n = 70)
p value, two-tailed	0.00	0.00	0.01
Father*			
Nonsmoker (n = 166)	84 ± 1.1	71 ± 2.0	1.90 ± 1.19 (n = 70)
Smoker (n = 86)	81 ± 2.3	86 ± 3.3	1.27 ± 1.80 (n = 34)
p value, two-tailed	0.21	0.46	0.14

*Information about smoking was available for 239 mothers and 232 fathers.

†The PC₂₀ was performed on all 104 children who were eligible for the test. T tests were carried out on logarithm of the PC₂₀ values.

Table 4—Correlation Between Indicators of Asthma Severity and Log of the Number of Cigarettes Smoked in the House by the Parents, and Probability (p) of $r = 0$

Feature	Recent Bronchodilators*	FEV ₁ %	FEF25-75%	PC ₂₀ †
Mother†				
r	0.12	-0.27	-0.27	-0.27
n	226	237	237	104
p	0.04	0.00	0.00	0.00
Father†				
r	-0.05	-0.06	-0.03	0.00
n	223	232	232	104
p	0.22	0.17	0.33	0.07

*Information about bronchodilators was not known in 9 (point Biserial correlation coefficient).

†The PC₂₀ was performed on all 104 children who were eligible for the test. T tests were carried out on logarithm of the PC₂₀ values.

‡The number of cigarettes smoked by the mother was available in 237 patients and by the father in 232.

$p = 0.045$). This observation suggests that cigarette smoke from the father also increases bronchial irritability in his child but that in the whole group the number of cigarettes smoked by the father was less accurately reported than the number smoked by the mother. A more accurate number for the mother is to be expected, as the history was provided by her alone in 71 percent, by the father alone in 8 percent, and by both together in 18 percent of participants. The disproportionate frequency with which the child was accompanied only by the mother suggested another reason for the good correlation between asthma severity and maternal but not paternal smoking. The mother spent more time than the father in caring for the child, and the child was therefore more intimately exposed to her cigarette smoke. Yet another possible reason for a lesser effect of the father's smoking habits was that he smoked fewer cigarettes (eight per day) when in the house than did the mother (ten per day).

As may be expected, if passive smoking aggravates asthma, the children of smoking mothers were more severely affected in the cold, wet season than in the warm, dry season. In the cold, wet season the FEV₁% was 14 percent lower in the children of smokers than in those of nonsmokers, and the FEF25-75% was 25 percent lower (Fig 2 and 3, Table 5). These differences were statistically highly significant. In children seen during the warm, dry season, by contrast, the FEV₁% and FEF25-75% were no lower in children of smokers than in those of nonsmokers. As predicted, spirometric test results were lower if children of smokers were seen in the cold, wet season than if seen in the warm, dry season: the mean FEV₁ was 15 percent lower (t value, -2.23, two tail probability, 0.03), and the FEF25-75% was 23 percent lower (t value, -1.94, two-tail probability, 0.057) (Table 5). A smaller number of children had data for PC₂₀ and for recent medication,

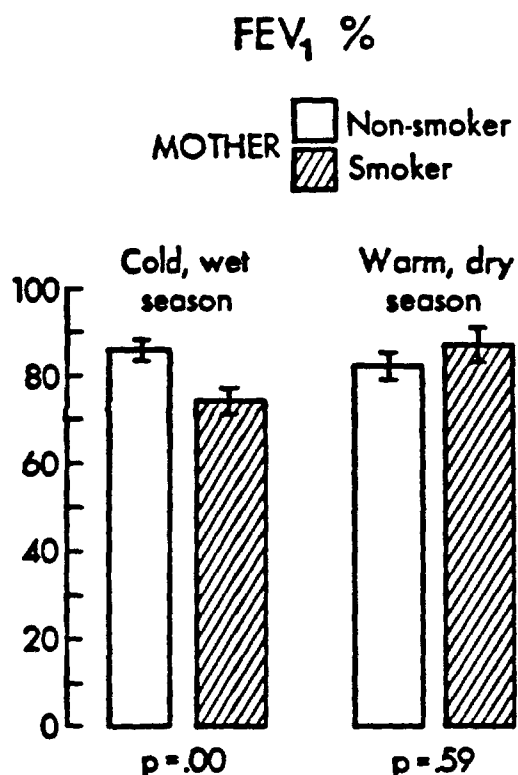


FIGURE 2. The mean FEV₁ % predicted in four groups of asthmatic children who were classified by their mother's smoking habits and the season in which they were seen.

but for these there was nonetheless a significant difference between children of smokers and nonsmokers, if seen in the cold, wet season. In this season the differences also tended to be greater than those observed in the warm, dry season (Tables 5 and 6).

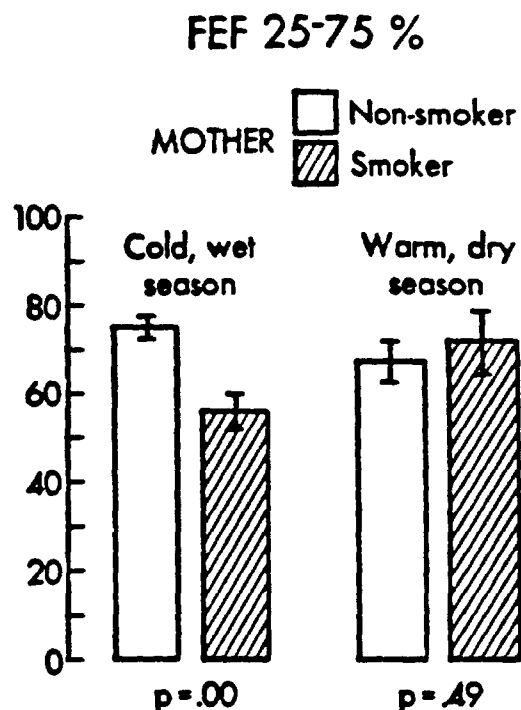


FIGURE 3. The mean FEF25-75% predicted in four groups of asthmatic children who were classified by their mother's smoking habits and the season in which they were seen.

As well, there was evidence of a dose-response to cigarette smoke during the cold and wet but not during the warm and dry months. In the cold, wet season there was a significant correlation between the log of the number of cigarettes the mother smoked while in the house and the likelihood of recent bronchodilator use, and also the extent of the decrease in FEV₁ % in

Table 5—The Difference Between Indicators of Asthma Severity in Children of Nonsmoking and Smoking Mothers When Measured in the Cold, Wet Season (October-May), Compared With the Warm, Dry Season (June-September)*

Season	FEV ₁ %	FEF25-75%	Geometric Mean PC ₂₀
October to May			
Mother nonsmoker (n = 141)	86 ± 1.2	75 ± 2.2	1.85 ± 1.18 (n = 61)
Mother smoker (n = 45)	74 ± 2.7	56 ± 3.8	0.85 ± 1.36 (n = 21)
t value	4.50	4.28	2.53
p (2-tail)	0.00	0.00	0.01
June to September			
Mother nonsmoker (n = 42)	82 ± 2.9	67 ± 4.5	2.37 ± 1.3 (n = 17)
Mother smoker (n = 11)	87 ± 3.6	72 ± 7.4	1.24 ± 2.1 (n = 5)
t value	-0.7	-0.55	1.02
p (2 tail)	0.49	0.59	0.32

*One subject was omitted from the analysis because the smoking status of the mother was not known. T tests were carried out on the logarithm of the PC₂₀ values. Mean ± standard errors are presented.

Table 6—The Seasonal Differences Between Nonsmoking Mothers' Children and Smoking Mothers' Children as to Whether They Had Taken Bronchodilator Medication Recently

Season	Recent Bronchodilator Medication*			
	Yes		No	
	No.	%	No.	%
October to May†				
Mother nonsmoker	34	25	102	75
Mother smoker	19	43	25	57
June to September‡				
Mother nonsmoker	16	40	24	60
Mother smoker	3	30	7	70

*Nine subjects were omitted from the analysis because it was not known whether they had taken bronchodilator medication recently.

† χ^2 4.45 (df = 1) p value (2-tailed) = 0.03.

‡ χ^2 0.05 (df = 1) p value (2-tailed) = 0.83.

FEF25-75%, and in the logarithm of the PC_{20} (Table 7). But during the warm, dry season there was no correlation between the number of cigarettes she smoked and any of these variables.

When multiple regression using FEV_1 , FEF25-75%, and log PC_{20} as the dependent variables was carried out for each season separately, the results of the univariate analysis were confirmed. The independent variables were sex, recent respiratory infection, recent medication, positive skin test, family history of asthma, hot air heating, wood stove, gas range, presence of household pets, mother's smoking habits, father's smoking habits, and the logarithm of age, duration of asthma, and number of siblings. In the cold, wet season the number of cigarettes that the mother smoked in the house was the most strongly predictive variable for all three measures of lung

Table 7—Correlation Between Indicators of Asthma Severity When Children Are Seen in the Cold, Wet Season Compared With the Warm, Dry Season, and the Logarithm of the Number of Cigarettes Smoked in the House by the Mother, and Probability (p) of $r = 0$

Season	Recent Bronchodilators*†	FEV_1 ‡	FEF25-75%‡	PC_{20} ‡
October-May				
r	0.17	-0.37	-0.35	-0.28
n	179	185	185	82
p	0.01	.00	.00	<.01
June-Sept				
r	-.06	.06	.04	-.23
n	49	82	82	22
p	.29	.28	.40	.15

*Nine subjects were omitted from the analysis because the respondent did not know whether they had received bronchodilators recently (Point Biserial correlation coefficient).

†Three subjects were omitted from this analysis because the respondent did not know how many cigarettes the mother smoked while in the home.

‡Logarithm of PC_{20} used for correlation.

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function. It was the only variable significantly related to FEF25-75% and to log PC_{20} . But in the case of FEV_1 , recent medication also had a significant effect. Conversely, in the warm, dry season, the number of cigarettes the mother smoked in the house had no significant relationship with any of the three measures of lung function. For FEV_1 , having a gas range was the only significant predictor but, for FEF25-75%, the duration of the child's asthma and having a gas range were equally strongly correlated with the dependent variable. None of the variables was significant predictors of log PC_{20} .

DISCUSSION

The results suggest that passive smoking in the home worsens bronchial irritability and narrows the bronchi in asthmatic children. These changes were more marked in the children of mothers who smoked, compared with those of mothers who did not smoke, as reported in our previous study.¹⁷ The likelihood that it was passive smoking that caused the increased severity of asthma in the children of smokers, rather than some other difference between them and the children of nonsmokers, was strengthened by the finding that the FEV_1 and FEF25-75% in children of smokers were lower only in the cold, wet season, the period when children are kept indoors, when energy is conserved by closing windows,^{12,13} and when concentrations of smoke in the house reach high levels because of decreased ventilation rates.^{12,13} During the cold, wet season there was also a significant correlation between the number of cigarettes the mother smoked in the house and the extent of the decrease in FEV_1 , FEF25-75%, and log PC_{20} (Table 7), indicating a dose-response relationship.

In the warm, dry season, by contrast, when children play outdoors and houses are well ventilated, spirometric test results were no lower in children of smokers than in those of nonsmokers, and in smokers' children the mean FEV_1 was higher in those seen in the warm, dry season than in those seen in the cold, wet months. Also, there was no correlation between the number of cigarettes the mother smoked in the house and any lung function test performed during the warm, dry season.

Although the numbers of data on bronchodilator use and PC_{20} are too small for conclusions, they indicate the same trend—that children of smokers have more severe asthma in the cold, wet season than in the warm, dry season.

In our study¹⁷ as in several others, there was little effect attributable to cigarette smoke from the father.^{2,3} This finding suggests that children inhale less smoke from their fathers' cigarettes than from their mothers', an explanation supported by the results of a study by

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Jarvis and colleagues.¹⁸ They reported that the mean cotinine level in the saliva of children is 1.95 ng/ml if only the mother smokes and 1.31 ng/ml if only the father smokes. Our study offers three possible reasons for maternal smoking being the more important. One is that fathers, on average, smoke fewer cigarettes in the house than mothers do. Another is that children are more intimately exposed to their mothers and to their cigarettes than to their fathers; the mother alone accompanied 71 percent of our subjects. Third, the number of cigarettes smoked in the house was less accurately reported for the father than for the mother; only the mother was present to provide the history in 71 percent of visits. Kolonel et al²⁰ found that a wife's estimate of the number of cigarettes her husband smokes is inaccurate: in only 54 percent of cases does it agree within five cigarettes per day with the husband's own estimate. It is, however, unlikely that mothers or fathers were incorrectly classified as smokers or nonsmokers. Kolonel et al²⁰ reported complete agreement in 95 percent of couples when the man and his wife are asked, separately, whether he is a smoker. A personal history of being a smoker or nonsmoker has also been shown to be accurate, using expired carbon monoxide and serum thiocyanate levels as markers of smoking,²¹ nor is it likely that a significant number of the children were incorrectly classified as nonsmokers.

To attribute the results of our study to an error of classification, one would have to postulate that nonsmokers' children are more honest than are smokers' children, and that smokers' children who are seen in the warm, dry season are more honest than are smokers' children seen in the cold, wet season. A more likely explanation for the low prevalence of active smokers in our patient population is that they are aware that cigarette smoke aggravates their asthma, and so they do not smoke. In support of this hypothesis is the finding by O'Connor et al²² that none of the asthmatic children in their survey was a smoker. When asked privately whether they are smokers, children usually give an honest answer. Pedersen et al²³ measured CO in expired air and found that 5.5 percent, at most, gave false information. Neither is it likely that a difference in social class or referral pattern accounted for the more severe asthma found in children of smoking mothers. Social class is usually determined by the father's occupation,²⁴ yet we found no relationship between the father's smoking habits and his child's spirometric test results, whereas there was a highly significant relationship between these results and the mother's smoking habits. If smoking mothers are more reluctant to take their children to a pediatric allergist than nonsmoking mothers, one would expect children of smokers to have had asthma for a greater number of years. This was not the case. There was no significant

difference between the two groups in the duration of the child's asthma.

Although there was no association between the father's smoking and the results of the children's spirometric tests, there was nonetheless some evidence that his smoke might be influencing bronchial irritability in the child. There was a significant correlation between the logarithm of the child's PC_{20} and the logarithm of the number of cigarettes the father himself said he smoked while in the house.

Greater exposure to other pollutants, such as combustion products from wood-burning stoves²⁵ or gas for cooking,²⁶ did not seem to account for the worsened asthma in the children of smoking mothers. Similar proportions in both groups used wood stoves for heating and gas stoves for cooking. Nor was there a significant difference between the two groups in ownership of pets, which might aggravate asthma in susceptible subjects, nor in the use of forced-air heating systems, which might circulate allergens.

Our demonstration that passive smoking affects asthma significantly only during the cold, wet season is consistent with results obtained in surveys of representative samples of schoolchildren in different regions of North America and in Britain. Those surveyed in Arizona, a warm, dry part of the United States,¹⁴ and those surveyed during the summer in Britain²⁷ showed no significant difference in spirometric test results between children of smokers and nonsmokers. Surveys conducted in areas with cold winters, by contrast, usually reveal significant differences between the two groups.¹⁴ But even in these areas, the difference in spirometric values between children of smoking mothers and nonsmoking mothers is small, not exceeding 5 percent, and is considerably smaller than in our study on asthmatic subjects, suggesting that representative groups of schoolchildren are less severely affected by maternal smoking than are asthmatic children.

Our finding that bronchial responsiveness is greater in asthmatic children of mothers who smoke than in those of mothers who do not smoke is also consistent with previously published articles. We reported earlier an increased bronchial responsiveness in children of smoking mothers in a group of 94 asthmatic children;¹⁷ such an increase was also subsequently noted in a community-based sample of 21 asthmatic children by O'Connor et al.²⁸

Passive smoking is likely to be the cause of the greater bronchial irritability and the increased bronchial obstruction which we find in asthmatic children of smoking mothers compared with those of nonsmoking mothers. Although children in the two groups are comparable in other respects and have similar indications of asthma severity during the warm, dry season when their houses are well ventilated, children of

smoking mothers have pulmonary function that is significantly poorer during the cold, wet season when houses are closed up, when indoor cigarette smoke reaches its highest level, and when the children spend more time in the house.

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Somerville, S.M., Rona, R.J., Chinn, S. "Passive smoking and respiratory conditions in primary school children" Journal of Epidemiology and Community Health 42: 105-110, 1988.

ABSTRACT. The effect of passive smoking on respiratory symptoms of children aged 5 to 11 years was investigated in over 4000 English children and nearly 800 Scottish children participating in the National Study of Health and Growth in 1982. After adjusting for associations of respiratory symptoms with age, sex, and a number of potentially confounding variables, significant associations were found of wheeze, both occasional and persistent, day or night cough, and bronchitis attacks with number of cigarettes smoked by parents at home for English children and for occasional wheeze in Scottish children. Asthma attacks and cough first thing in the morning showed positive but not statistically significant associations in English children. The presence of at least one condition was statistically significant in both English and Scottish children. The largest relative risk for exposure to 20 cigarettes a day compared to no exposure was 1.60 for persistent wheeze in English children (95% confidence interval 1.17-2.18).

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Passive smoking and respiratory conditions in primary school children

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SUMMARY The effect of passive smoking on respiratory symptoms of children aged 5 to 11 years was investigated in over 4000 English children and nearly 800 Scottish children participating in the National Study of Health and Growth in 1982. After adjusting for associations of respiratory symptoms with age, sex, and a number of potentially confounding variables, significant associations were found of wheeze, both occasional and persistent, day or night cough, and bronchitis attacks with number of cigarettes smoked by parents at home for English children and for occasional wheeze in Scottish children. Asthma attacks and cough first thing in the morning showed positive but not statistically significant associations in English children. The presence of at least one condition was statistically significant in both English and Scottish children. The largest relative risk for exposure to 20 cigarettes a day compared to no exposure was 1.60 for persistent wheeze in English children (95% confidence interval 1.17-2.18).

Among the harmful effects postulated for passive smoking is a possible association between parental smoking and respiratory conditions in children, which has been investigated in a large number of studies. A review article¹ concluded that the studies were consistent in suggesting increased infections in children under 1 year of age but inconsistent in older children. As almost all found some effect of parental smoking, the latter conclusion seems to have been due to the lack of a significant dose-response relation in just over half the studies considered.

The studies on older children have varied in the symptoms studied, in the age range of the children, in the proportion of parents who smoked, and in the potentially confounding variables that have been taken into account. A report of a workshop on the effect of passive smoking on children² listed nine groups of such variables that it is desirable to take into account. No study has included all of these, and most included only a few variables in one or two of the listed groups. This can be attributed largely to the fact that few² of the studies were designed to investigate passive smoking effects, and were opportune analyses on data collected mainly to investigate the relations in children between symptoms and lung function and a variety of environmental factors.

Of even more importance to the detection of a dose-response relation the studies have differed

markedly in size and in the measure of passive smoking. The most usual measure was the number of parents smoking, providing lower power to detect a dose-response relation than a measure of the amount smoked. A recent review³ reported only three studies of young children in which the measure of passive smoking was cigarettes smoked per day, and just one study of older children.

The National Study of Health and Growth, an on-going surveillance study of the health and growth of primary school children in England and Scotland, was also not designed to investigate passive smoking effects. Data on the number of smokers of five or more cigarettes a day in the child's home were collected in 1977 as a confounding variable in a study of the relation of respiratory illness and outdoor air pollution.⁴ These data also suggested a negative relation of child's height to number of smokers in the home after adjusting for birthweight.⁵ In order to study this association further, data on the number of cigarettes smoked at home by each parent, and by the mother during pregnancy, were collected in 1982.⁶ No data on lung function were obtained.

Further examination of the 1977 data on English and Scottish children showed a number of statistically significant positive associations of respiratory symptoms with the number of smokers. Given the reasonable sample size, the availability of data for a

Table 1 Number of children for whom data on each respiratory condition were obtained and the prevalence (%) of each condition, by sex and country

Respiratory condition	England				Scotland			
	Boys		Girls		Boys		Girls	
	No	Prevalence %	No	Prevalence %	No	Prevalence %	No	Prevalence %
Chest EVER sound wheezy or whistling	3063	12.6	2870	9.5	572	13.1	563	6.9
Chest wheezy or whistling on MOST days or nights	3046	3.2	2858	2.4	569	4.4	564	2.8
In the last 12 months had:								
Bronchitis attack(s)	3030	4.0	2852	2.7	570	3.5	565	2.1
Asthma attack(s)	3060	4.2	2862	2.8	568	2.3	567	2.1
Usually coughs first thing in the morning	3048	4.2	2851	4.5	569	5.1	558	5.0
Usually coughs during the day or at night	3036	8.3	2858	7.8	568	11.1	560	8.4

number of potentially confounding variables, and the almost unique data on amount of smoking in the home, it was decided to investigate the dose-response relation of symptoms to passive smoking, using the 1982 data, in children aged 5 to 11 years.

Methods

In 1982 children took part in the study in 22 areas in England and five in Scotland. Data on the child's respiratory symptoms, parental smoking, and family background were obtained from a self-administered questionnaire completed by the child's mother. Triceps skinfold thickness was measured as described elsewhere⁷ and was included in the analysis as previously⁸ a relation had been shown between respiratory symptoms and this measure of obesity.

Each of six respiratory symptoms or illnesses, given in table 1, was analysed as a dichotomous, ie, present or absent, dependent variable using logistic regression. Any child with a missing value was excluded from the analysis of that symptom. The number of cigarettes smoked per day at home by the mother and father in total, the passive smoking component, and the number of cigarettes smoked per day by the mother during pregnancy with the child were each included as a quantitative variable. Two groups of potentially confounding variables were included in the regression analyses, those treated as quantitative variables and those that were categorical variables. The former group consisted of the child's age, birthweight, triceps skinfold thickness expressed as a standard deviation score,⁷ mother's age, and number of siblings. The categorical variables were: child's sex; father's social class, in four groups as non-manual, skilled manual, semi-skilled or unskilled manual, or other; father employed, unemployed or not known; child in one-parent family, two-parent, or not known; presence or

absence of household overcrowding, defined as a ratio of people in the household to number of rooms of at least 1.25; mother's education as highest full-time level in seven groups, none or primary only, secondary or comprehensive school, grammar, technical or commercial college, university, other, or not known. Except as stated missing data excluded a child from the analysis.

Analyses were carried out with all these as independent variables and also with just parental smoking, age, and sex as the independent variables, for England and Scotland separately, and for the two countries combined. Analyses were also carried out for each sex separately and, using the fully adjusted model, with the dependent variable as presence of at least one of the respiratory conditions.

Results

In 1982 there were 8118 children eligible to take part in the study; a questionnaire was returned for 87.8% of these children.

Table 2 Distribution of cigarettes smoked per day by parents at home in England and Scotland

No. of cigarettes (total smoked by father and mother)	% of parents	
	England	Scotland
0	57.9	59.9
≤4	3.4	3.0
5-14	16.9	19.9
15-24	12.4	19.7
25-34	5.2	9.2
≥35	4.2	8.4
No. of children whose parents are included in this table	5169 (100%)	928 (100%)

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Table 3 Results of logistic regression analyses for England showing the association between respiratory symptoms and passive smoking[#] from the fully adjusted model

Respiratory symptom	Regression coefficient \pm standard error		
	Boys (N = 218 to 2206)	Girls (N = 2074 to 2128)	All children (N = 4255 to 4371)
Chest EVER sound wheezy or whistling	0.008 \pm 0.007	0.014* \pm 0.008	0.011* \pm 0.005
Chest wheezy or whistling MOST days or nights	0.037** \pm 0.011	0.010 \pm 0.013	0.024** \pm 0.008
In the last 12 months had Bronchitis attack(s)	0.004 \pm 0.012	0.033* \pm 0.013	0.018* \pm 0.008
Asthma attack(s)	-0.005 \pm 0.012	0.026* \pm 0.013	0.009 \pm 0.009
Usually coughs first thing in the morning	-0.002 \pm 0.012	0.022* \pm 0.011	0.012 \pm 0.008
Usually coughs during the day or at night	0.007 \pm 0.008	0.020* \pm 0.008	0.013* \pm 0.006
At least one condition	0.008 \pm 0.006	0.011 \pm 0.007	0.009* \pm 0.005

* $p < 0.1$ * $p < 0.05$ ** $p < 0.01$ [#] parental smoking defined as the total number of cigarettes smoked at home by mother and father together

PREVALENCE OF RESPIRATORY CONDITIONS

Table 1 shows the number of children for whom data were obtained on each respiratory condition, which varied from 86.4% to 87.1% of the total eligible, and the percentage with each condition, by sex and country. The prevalence of each condition was greater in boys than in girls but differed little between England and Scotland.

DISTRIBUTION OF PASSIVE SMOKING

Data on parental smoking were available for 75.1% of children. The distributions of the number of cigarettes smoked per day by the parents at home are given in table 2 for children in England and Scotland. Smoking by parents was more prevalent in Scotland than in England.

RELATION OF RESPIRATORY CONDITIONS TO PASSIVE SMOKING

After exclusions for missing data, primarily in respiratory symptoms or parental smoking, the number of children available ranged from 4337 (63.4%) to 4371 (63.9%) for England and from 766 (60.90%) to 771 (61.3%) for Scotland. Table 3 shows the relation of six respiratory conditions to passive smoking for English children as estimated from the logistic regression analysis, adjusted for all the potentially confounding variables listed above. For all children parental smoking was most strongly positively associated with 'chest wheezy or whistling on most days or nights' ($p < 0.01$) and also significantly associated ($p < 0.05$) with 'usually coughs during the day or night', 'chest ever sounds wheezy or whistling', and bronchitis attacks in the last 12 months. The relation was positive for the other two conditions. Although results appeared to show some differences between boys and girls, no significant

difference, as assessed from an interaction term in the model, was found in the relation of passive smoking except for asthma ($p < 0.05$), which showed a positive association ($p < 0.1$) with parental smoking in girls, and a non-significant negative relation in boys. The relation of prevalence of at least one of the conditions was just significant ($p < 0.05$) for all English children.

For Scottish children, who were fewer in number than the English children, the only significant relation of an individual condition to parental smoking was found for 'chest ever wheezy' ($p < 0.01$). However the prevalence of at least one condition was significantly related to parental smoking ($p < 0.05$).

Results are given for England and Scotland separately as the relation of 'chest ever wheezy' and 'wheeze most days or nights' to passive smoking was found to differ significantly between the two countries ($p < 0.05$). 'Wheeze most days or nights' showed a relation to passive smoking only in England, whereas 'chest ever wheezy' showed a stronger relation to passive smoking in Scottish children than in English, of similar size to that for persistent wheeze in English children.

EFFECTS OF ADJUSTMENT FOR CONFOUNDING VARIABLES

Table 4 shows the relation between passive smoking and each respiratory condition adjusted only for age for boys and girls separately, and for age and sex for all English children. Comparison with table 3 shows that in most cases adjustment for the potentially confounding variables generally increased the standard errors so there was a reduction in statistical significance, the notable exceptions being 'chest wheezy or whistling most days or nights' in boys, and bronchitis attacks in girls for which the regression coefficient increased considerably on adjustment. For

Table 4 Results of logistic regression analyses for England showing the association between respiratory symptoms and parental smoking for the model adjusted only for age (and sex for all children)

Respiratory symptom	Regression coefficients \pm standard error		
	Boys (N = 2181 to 2246)	Girls (N = 2074 to 2128)	All children (N = 4255 to 4371)
Chest EVER sound wheezy or whistling	-0.002 \pm 0.006	0.013* \pm 0.006	0.005 \pm 0.004
Chest wheezy or whistling MOST days or nights	0.023* \pm 0.009	0.033** \pm 0.009	0.028*** \pm 0.007
In the last 12 months had: Bronchitis attack(s)	-0.002 \pm 0.010	0.022* \pm 0.010	0.008 \pm 0.007
Asthma attack(s)	-0.014 \pm 0.010	0.018* \pm 0.010	0.000 \pm 0.007
Usually coughs first thing in the morning	0.001 \pm 0.010	0.021* \pm 0.006	0.012* \pm 0.006
Usually coughs during the day or at night	0.015* \pm 0.006	0.026*** \pm 0.006	0.021*** \pm 0.004
At least one condition	0.005 \pm 0.005	0.012* \pm 0.006	0.008* \pm 0.004

N = the range of the number of children in the six analyses
 * $p < 0.1$ $p < 0.05$ $p < 0.01$ $p < 0.001$

See footnote to Table 3.

Table 5 Estimates of prevalence (%) of respiratory symptoms and relative risk for children* of parents smoking no cigarettes, 10 and 20 cigarettes at home per day, based on the fully adjusted model for all children

Respiratory condition	Prevalence % (relative risk compared to non-smoking parents)		
	Cigarettes smoked at home by parents		
	0	10	20
Chest wheezy or whistling on MOST days or nights	2.8	3.5 (1.27)	4.5 (1.60)
Bronchitis attack(s) in the last 12 months	3.9	4.7 (1.18)	5.5 (1.40)
Usually coughs during the day or night	7.7	8.7 (1.13)	9.8 (1.27)
At least one condition	17.9	19.3 (1.08)	20.8 (1.16)

* Given for boys aged 8 years, with no siblings, in a two parent family, father employed and social class IIIB, mother's smoking in pregnancy 0, home not overcrowded, mother aged 32 and educated at a secondary or comprehensive school, thoracic skinfold standard deviation score 0, birthweight 3000 g

all Scottish children, adjusting only for age and sex, significant associations were found between passive smoking and 'chest ever wheezy' ($p < 0.01$), 'usually coughs during the day or night' ($p < 0.05$), and prevalence of at least one condition ($p < 0.01$).

ESTIMATES OF RELATIVE RISK

Table 5 gives examples of prevalence of respiratory conditions and relative risk (in parentheses) estimated from the regression coefficients in the fully adjusted model for the three conditions showing the largest associations with passive smoking in all English children. Compared with children whose parents do not smoke the relative risks were around 1.2 for children whose parents smoke 10 cigarettes a day in total at home, and from 1.3 to 1.6 for those whose parents smoke 20 a day. They are of necessity given for fixed values of the other independent variables but would not differ markedly for different values of these variables. The relative risk of at least one condition is

lower, only just significantly different from 1.0 at the 5% level, but shows the estimated increase in the percentage of children suffering some respiratory symptom at the given levels of parental smoking.

Discussion

A number of statistically significant positive associations were found between respiratory conditions in children and number of cigarettes smoked per day at home by their parents, but not consistently for all symptoms or in both countries. The result also differed to some extent from those found in the 1977 data, in which the passive smoking variable, number of smokers of at least five cigarettes a day in the home, was significantly associated ($p < 0.05$) with all six conditions except bronchitis in the last 12 months. The analyses of the two years' data differed in the confounding variables taken into account, the use of gas for cooking and population density being

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included in the 1977 analysis, but not maternal smoking in pregnancy or mother's education or age. They were similar in the age range of the children, in sample size, and in the wording of the questions about respiratory conditions.

Inevitably, other studies have differed in the symptoms or illnesses studied and in the exact questions asked. However the largest study with a similar age range,⁹ in which 10 106 children aged 6 to 10 years were involved, found highly significant associations ($p < 0.001$) between cough for three months or more of the previous year and wheeze most days or nights with maternal smoking, and a less significant association ($p < 0.01$) of bronchitis with maternal smoking, broadly in line with our findings.

Other studies have also found significant positive associations between persistent cough and parental smoking,¹⁰⁻¹² and, although not statistically significant, a relative risk of 4.9 for persistent wheeze was found for children exposed to a smoker at home compared to those never exposed in a study of 626 children under 15 years.¹²

The only other study¹³ to include 'cough first thing in the morning' found a positive association ($p < 0.05$) in 12 year old girls after allowing for the child's own smoking. Many studies of passive smoking have included non-persistent wheeze, with various definitions, and some asthma or bronchitis. About half of those obtained significant positive associations, and the rest non-significant associations. However, few studies have included all four symptoms of wheeze, cough, asthma, and bronchitis. Apart from the question of prime importance being whether passive smoking causes any harmful effect to children of primary school age, the nature of the effect being a secondary consideration, the symptoms are not manifestations of distinct diseases. Analysis of single symptoms may fail to detect a real increase in the prevalence of a condition. In particular, an effect of passive smoking increasing symptoms of asthma may be missed if only a question about asthma is included due to underdiagnosis in many children with wheeze^{14 15} and the fact that cough may be the only presenting symptom.¹⁶

No data were available on active smoking by the children as the questionnaire was completed by a parent. However, even in the oldest age group and on the assumption that smoking by the child is strongly associated with parental smoking, the prevalence of active smoking would be too small to account for the differences in prevalence of respiratory symptoms. Dobbs and Marsh¹⁷ reported a prevalence of regular smoking, defined as 'at least one cigarette a week', of 1% and 0% in first year secondary school boys and girls respectively, in England in 1982, and 5% and 3% in Scotland. Of the groups of other confounding

variables that have been suggested² that are relevant to children's symptoms as reported by the mother, those of other indoor pollutants are probably the most important ones not included in the analysis of the 1982 data. In the analysis of 1977 data the use of gas for cooking, an important source of nitrogen dioxide in the home,¹⁸ did not eliminate positive associations of respiratory symptoms with passive smoking.

Parental symptoms are on the list of potentially confounding variables,² and there is no doubt that a child's symptoms show a relation to these.^{9 10 12 19} However, as many of the symptoms of smokers will be a result of their smoking, adjustment for parental symptoms could remove a real effect of parental smoking on a child's health.²⁰ Of the few studies in which the adjustment had been made the largest^{9 20} still found positive associations between child's cough and wheeze and maternal smoking in over 10 000 6-10 year old children. Lebowitz,¹² in a much smaller study, found statistical significance of an association removed by the adjustment. Schenker *et al*¹⁹ found a positive association between chest illness on at least three days in the last year which persisted on adjustment for parental respiratory disease, but found no association before or after adjustment in chronic cough, phlegm or wheeze in 4000 children aged 5 to 14.

Studies have varied in the prevalence of respiratory conditions and in the percentage of parents smoking. While low values of either may lead to statistically insignificant results in the presence of a real effect, the most important variation in the studies has been in sample size. The majority of studies provide no information on the amount smoked by parents. For children of two parents who smoke the estimated relative risk of the respiratory conditions studied was less than two compared to children of non-smoking parents in almost all studies.³ The conclusion that emerges is that if there is a real effect of passive smoking on the respiratory health of children aged 5 to 11 years, then it is a small one, and a large study is required for a high probability of its detection. Although results for the smaller sample of Scottish children were not significantly different from those for English children, except for wheeze, a significant relation was found only for 'chest ever wheeze' and at least one condition. For English children the largest relative risk was for persistent wheeze, of 1.60 in children whose parents smoked a total of 20 cigarettes a day (95% confidence interval 1.17-2.18) and 1.16 (1.00-1.34) for any symptom. The USA six cities study⁹ found a relative risk of 1.3 for persistent wheeze in 6 to 10 year old children whose mothers smoke 20 cigarettes a day.

As the association is probably less strong than that for children under 1 year, it is to be expected that secondary school children would show a weaker, or no

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association of symptoms with passive smoking. We have therefore confined consideration of the literature to studies including broadly similar age groups. All four studies^{9 13 21 22} that we have identified with an analysis of data for 6000 or more children in a similar age range to those in our 1982 English sample have shown at least one significant positive association with passive smoking. The two largest^{21 22} also showed a dose-response relation. Our data have supported the hypothesis of an effect of parental smoking on children of this age. Scepticism could be removed further only by a study of several symptoms in at least 6000 children, including all potentially confounding variables as recommended,² with a quantitative measure of passive smoking by the child.

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Strachan, D.P. "Damp housing and childhood asthma: validation of reporting of symptoms" BMJ 297: 1223-1226, 1988.

ABSTRACT. The relations among parental reports of respiratory symptoms, bronchospasm measured after exercise, and the presence of visible fungal mould in the home was assessed in a population sample of 7 year old children (n=873). Wheeze in the past year was the symptom most closely associated with reported dampness and particularly with mould. The unadjusted odds ratio relating mould and wheeze was 3.70 (95% confidence interval 2.22 to 6.15), and after adjustment for housing tenure, number of people per room, number of smokers in the household, and gas cooking this remained highly significant (odds ratio 3.00 (1.72 to 5.25)). The reduction in forced expiratory volume in one second after six minutes of free running was used to validate reporting of wheeze. At all levels of measured bronchial lability wheeze was reported more commonly in the children from homes with mould. There was no significant difference in the degree of bronchospasm measured among children from homes with and without mould.

Awareness of dampness or mould in the home may be a determinant of parental reporting of symptoms and may account for much of the observed association between mould and respiratory symptoms.

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Damp housing and childhood asthma: validation of reporting of symptoms

D P Strachan

Abstract

The relations among parental reports of respiratory symptoms, bronchospasm measured after exercise, and the presence of visible fungal mould in the home was assessed in a population sample of 7 year old children ($n=873$). Wheeze in the past year was the symptom most closely associated with reported dampness and particularly with mould. The unadjusted odds ratio relating mould and wheeze was 3.70 (95% confidence interval 2.22 to 6.15), and after adjustment for housing tenure, number of people per room, number of smokers in the household, and gas cooking this remained highly significant (odds ratio 3.00 (1.72 to 5.25)). The reduction in forced expiratory volume in one second after six minutes of free running was used to validate reporting of wheeze. At all levels of measured bronchial lability wheeze was reported more commonly in the children from homes with mould. There was no significant difference in the degree of bronchospasm measured among children from homes with and without mould.

Awareness of dampness or mould in the home may be a determinant of parental reporting of symptoms and may account for much of the observed association between mould and respiratory symptoms.

Introduction

In industrialised countries people spend much of their life indoors, and interest in the public health effects of the indoor environment is growing.¹ Children are particularly appropriate for investigation of the influence of environmental variables on respiratory disease because active smoking and occupational variables are excluded. Much attention has focused on the potential hazards from passive exposure to tobacco smoke²⁻⁴ and from nitrogen dioxide produced by gas cookers, unvented gas appliances, and paraffin heaters.^{5,7}

A common cause of complaint to landlords and local authorities is condensation of moisture from humid indoor air on to cold surfaces, which forms unsightly damp patches and promotes the growth of fungal moulds.⁸ Surveys in Scotland and England have suggested that between one quarter and one third of homes may be affected to some degree.^{9,10} Poor quality housing in general and dampness in particular are widely believed to be detrimental to respiratory health.¹¹ Allergic reactions to house dust mites, which thrive in damp homes,¹² or to the airborne spores of fungal moulds¹³ are plausible mechanisms for a causal link between damp conditions and symptoms related to asthma.

Few epidemiological studies have investigated this association, but two small studies in north west Edinburgh showed a positive relation between reported dampness and mould and respiratory symptoms in children.^{14,15} Similar findings have been reported in adults.^{16,17} Dampness (assessed

independently by environmental health officers) and high ambient humidity were found more commonly in the homes of children with respiratory symptoms,^{14,15} which indicated that reporting of housing conditions was not substantially biased by the presence of disease in the child. On the other hand, when consultations with general practitioners for respiratory complaints were used to validate reporting of symptoms there was no association with reported dampness or mould.¹⁶ This raised the possibility that symptoms were reported differently according to parents' perception of their home environment.

My study was designed to investigate damp, mouldy housing as a determinant of childhood asthma in a representative sample of the general population and to evaluate the role of differential reporting of symptoms in any association. In view of the limitations of general practice records for this purpose the symptoms were validated by physiological tests to detect abnormal reactivity of the airways.¹⁸

Subjects and methods

A random sample of one in three primary schools within the Edinburgh city boundary was obtained. The parents of all children in their third primary school year (age 6½-7½ years) were contacted by post in November 1986. A questionnaire asked about respiratory symptoms experienced by the child in the past year, including wheeze (defined as breathing that makes a high pitched whistling sound), a tendency for colds to go to the chest, sore throat, pain or discharge in the ear, and hay fever or frequent sneezing attacks. Parents were also asked how many nights the child had been kept awake by coughing during the previous month and how many days in the month the child had been troubled by daytime cough or by a blocked or running nose. Information was sought about conditions in the home, particularly the number of cigarette smokers in the household, the fuels used for heating and cooking, the formation of condensation or damp patches on walls, and the presence of mould or fungus.

Consent was requested for medical tests on the child at school, and the study received ethical approval from Lothian Health Board and Lothian Regional Council Education Department. Ventilatory function was measured with a pneumotachograph (Compact; Vitalograph, Buckingham), and spirometry was performed with the child standing and without nose clips; I supervised all measurements using the protocol of the American Thoracic Society.¹⁹ Measurements were taken before and five and 10 minutes after six minutes of free running in a corridor or classroom; the best of three recordings on each occasion was used. An index of bronchial lability induced by exercise was calculated as the minimum of the two measurements of forced expiratory volume in one second taken after exercise divided by the forced expiratory volume in one

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second obtained before exercise. Tests were performed at least six hours after a dose of inhaled bronchodilator. Eleven children were taking inhaled steroids or oral drugs for asthma; their results were analysed separately.

Routine statistical analysis was performed with the Statistical Analysis System.²² To explore in more detail the relations between symptoms and housing conditions and between mould, wheeze, and bronchial lability multiple logistic regression models were analysed with the generalised linear interactive modelling system.²³

Results

The parents of 1095 children received a questionnaire, and usable replies were obtained for 1012. Information on respiratory symptoms and housing conditions was available for 926-1004, depending on the detail required. Parental consent for clinical testing was obtained for 941 children. Twenty of these were included in pilot studies, and a further 20 moved to a different school before testing. Of the remaining 901 children, 892 were examined and 881 performed a satisfactory exercise test.

Complete information on dampness, mould, wheeze, and bronchial lability was available for 873 children (80% of the original sample, 97% of those eligible for testing). The prevalences of wheeze in the past year (12.7%; 111/873) and exposure to mould in the home (9.3%; 81/873) were somewhat higher in this group than among those with incomplete information (10.0% (13/130) and 6.3% (8/127), respectively).

Table 1 relates respiratory symptoms to various aspects of the home environment. The prevalences of wheeze and chesty colds were higher by a factor of between two and three among the children from homes reported to be affected by damp patches on walls or by mould; the higher prevalences among children sleeping in damp or mouldy bedrooms might be interpreted as evidence of a dose-response relation. Cough at night and during the daytime was significantly more common among children sleeping in damp bedrooms ($p < 0.001$ and $p < 0.05$, respectively), and a smaller excess was observed in children sleeping in bedrooms affected by mould. Mould in the child's

bedroom was significantly related to frequent trouble with a blocked or running nose ($p < 0.05$). The prevalences of cough at night and chesty colds were associated with crowding and the presence of smokers in the household. Domestic fuels were not important influences on the prevalence of respiratory symptoms. Paradoxically, chesty colds were considerably less common in children in households using gas for cooking but more prevalent in the small number of children exposed to unvented gas heating appliances. These relations in part reflected differences in the use of fuels by owner occupiers and tenants of rented housing. The pattern of association between dampness and hay fever was inconsistent; the difference in prevalence between all damp homes considered together and homes not affected was negligible ($\chi^2 = 0.54$, $df = 1$).

The association between damp, mouldy housing and wheeze was remarkable in view of the lack of a relation of wheeze to other environmental factors in the home. Compared with rented homes, owner occupied homes were less likely to be affected by dampness (83% (58/700) v 29.7% (89/300)) or mould (4.9% (34/700) v 18.3% (55/300)); this accounted for the difference in the prevalence of wheeze by housing tenure. In homes not affected by damp or mould the prevalence of wheeze was similar in the rented sector (11.1%; 23/207) and in owner occupied homes (10.6%; 67/631). By contrast, chesty colds, cough at night, cough during the day, and running nose were influenced by the number of people per room and the number of smokers in the household, factors that were strongly related to tenure and were therefore potential confounders for the relation to dampness or mould.

Possible confounding effects were investigated by multiple logistic regression models with wheeze in the past year as the outcome variable. The unadjusted odds ratio for mould anywhere in the home was 3.70 (95% confidence interval 2.22 to 6.15; $\chi^2 = 27.7$, $df = 1$). In a model that included housing tenure, number of smokers in the household, number of people per room, and gas cooking the odds ratio for mould was 3.00 (1.72 to 5.25; $\chi^2 = 15.2$, $df = 1$). The effect of mould was independent of housing tenure (χ^2 for interaction term = 0.41, $df = 1$). There was a close correlation

TABLE 1—Prevalence (%) of respiratory symptoms related to home environment. Numbers of children are given in parentheses

	Wheeze (during past year)	Chesty colds (during past year)	Cough at night (≥ 3 nights in past month)	Cough during day (≥ 3 days in past month)	Running nose (≥ 7 days in past month)	Hay fever (during past year)	Ear trouble (during past year)	Sore throat (during past year)
Tenure:								
Owners	10.7 (75/702)	13.5 (93/690)	7.8 (54/692)	13.2 (91/689)	12.5 (85/682)	10.8 (74/684)	24.1 (165/685)	50.4 (348/691)
Renting	16.3* (49/301)	27.4*** (80/292)	22.5*** (66/293)	22.0*** (63/286)	19.0* (54/284)	8.5 (24/281)	24.3 (70/288)	56.3 (166/295)
People per room:								
<1.0	11.5 (39/338)	15.6 (52/334)	8.0 (27/336)	13.4 (45/335)	12.4 (41/331)	9.6 (32/332)	26.3 (88/334)	51.2 (172/336)
1-1.5	13.3 (66/496)	17.2 (84/487)	13.0* (63/486)	17.1 (83/484)	16.1 (77/477)	10.5 (50/478)	22.1 (106/480)	51.9 (252/486)
>1.5	11.1 (14/126)	25.0* (31/124)	18.7** (23/123)	15.4 (18/117)	13.6 (16/118)	10.8 (13/120)	23.0 (28/122)	54.4 (68/125)
Smokers in household:								
0	12.1 (64/530)	14.8 (77/519)	9.0 (47/523)	13.9 (72/519)	10.9 (56/513)	10.2 (53/518)	23.5 (122/519)	51.1 (268/524)
1	12.1 (37/307)	18.4 (55/299)	14.0* (42/301)	16.5 (49/297)	17.2* (51/297)	10.3 (30/290)	25.3 (75/296)	52.5 (158/301)
≥ 2	13.4 (22/164)	25.3** (41/162)	19.5*** (31/159)	20.4 (32/157)	20.1** (31/154)	9.7 (15/155)	24.4 (38/156)	55.3 (88/159)
Gas cooker:								
No	13.0 (55/422)	21.0 (87/414)	13.5 (56/415)	15.3 (63/411)	14.7 (59/402)	10.6 (43/405)	21.9 (89/407)	53.1 (220/414)
Yes	11.7 (68/579)	15.2* (86/566)	11.2 (64/569)	16.0 (90/563)	14.2 (80/564)	9.7 (54/558)	25.9 (146/564)	51.4 (293/570)
Bottled gas stove:								
No	12.4 (114/920)	16.8 (151/901)	11.9 (108/905)	15.8 (141/895)	14.5 (129/887)	10.2 (91/889)	24.0 (214/892)	51.7 (467/904)
Yes	12.8 (10/78)	27.6* (21/76)	13.2 (10/76)	14.3 (11/77)	10.8 (8/74)	9.7 (7/72)	23.7 (18/76)	55.8 (43/77)
Paraffin heater:								
No	12.4 (121/974)	17.6 (168/953)	11.8 (113/958)	15.6 (148/949)	14.0 (131/939)	10.4 (97/937)	24.1 (228/945)	52.0 (498/958)
Yes	12.5 (3/24)	16.7 (4/24)	21.7 (5/23)	17.4 (4/23)	27.3 (6/22)	4.2 (1/24)	17.4 (4/23)	52.2 (12/23)
Coal fire:								
No	12.5 (117/937)	17.5 (161/918)	11.7 (108/921)	15.2 (139/912)	13.7 (124/904)	10.4 (94/903)	23.7 (215/909)	51.6 (475/920)
Yes	11.5 (7/61)	18.7 (11/59)	21.7 (5/23)	17.4 (4/23)	22.8 (13/57)	6.9 (4/58)	28.8 (17/59)	57.4 (35/61)
Damp:								
None	10.4 (90/853)	15.3 (128/839)	10.7 (90/841)	14.7 (123/834)	13.8 (114/824)	9.7 (80/824)	23.8 (197/829)	50.8 (427/840)
Other room†	20.9** (18/86)	25.6* (21/82)	11.1 (9/81)	18.5 (15/81)	17.3 (14/81)	14.3** (12/84)	32.1 (27/84)	60.0 (51/85)
Child's bedroom	24.6** (15/61)	37.3*** (22/59)	31.1*** (19/61)	25.9* (15/58)	17.2 (10/58)	8.9 (5/56)	18.3 (11/60)	56.7 (34/60)
Mould:								
None	10.5 (96/911)	15.6 (140/895)	11.7 (105/896)	15.3 (136/889)	13.3 (117/878)	9.8 (86/882)	23.2 (206/888)	52.1 (468/899)
Other room†	23.4* (11/47)	32.6** (15/46)	12.8 (6/47)	17.0 (8/47)	23.4 (11/47)	20.0 (9/45)	35.6 (16/45)	46.7 (21/45)
Child's bedroom	38.1*** (16/42)	43.6*** (17/39)	21.4 (9/42)	26.3 (10/38)	26.3* (10/38)	7.9 (3/38)	30.8 (12/39)	55.0 (22/40)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with prevalence in uppermost category.

†Present in one or more rooms other than child's bedroom.

between damp walls and mould: 48% (71/147) of the homes affected by dampness were reported to be mouldy, and 80% (71/89) of the mouldy homes were reported to be damp. Mould seemed to have a greater effect on wheeze than did damp. In a model that included damp walls anywhere in the house the effect of mould remained significant ($\chi^2=7.52$, $df=1$), whereas the effect of dampness independent of mould was negligible ($\chi^2=0.60$, $df=1$).

The relations between housing conditions and chest colds, cough at night, cough during the day, and nasal discharge were investigated in similar multiple logistic regression models with each respiratory symptom in turn as the outcome variable. The association between mould and chest colds was independent of housing tenure, number of people per room, number of smokers, and gas cooking (odds ratio 2.08 (1.22-3.51); $\chi^2=7.26$, $df=1$). Inclusion of wheeze during the past year as a further explanatory variable reduced this effect so that it was no longer significant, although it remained in the same direction (odds ratio 1.43 (0.77 to 2.70)). At least part of the association between chesty colds and mould thus seemed to be a consequence of a recent tendency to wheeze.

The weaker associations of cough at night and during the day with mould in the home were entirely explained by their common association with rented housing. After adjustment for tenure the odds ratios for cough at night and cough during the day associated with mould were 0.92 and 0.95, respectively, and the effect of mould on nasal discharge remained in the expected direction but was non-significant (odds ratio 1.61 (0.89 to 2.90); $\chi^2=2.42$, $df=1$). Further adjustment for the effects of number of people per room, number of smokers, and gas cooking made little difference to these results.

Objective evidence of airways reactivity was collected to investigate the possible contribution of bias in reporting to the observed association between wheeze and mould in data from this and a previous questionnaire.¹⁷ As expected, wheeze during the past year was more prevalent among the children who had bronchospasm after exercise. If no reporting bias had existed this relation would have been independent of housing conditions. In fact, for any given degree of bronchial lability a parental report of wheezing was more commonly obtained for children from homes with mould (table II). In a logistic regression model with wheeze during the past year as the outcome bronchial lability was included as a continuous explanatory variable. Its relation to wheeze was roughly linear (χ^2 for quadratic term=1.05, $df=1$) and was modelled as such. The effect of mould in the home was independent of lability (odds ratio 3.50 (1.95-6.47); $\chi^2=16.1$, $df=1$) and constant across the range of lability observed (χ^2 for interaction term=0.10, $df=1$). This odds ratio of 3.5 was comparable with the odds ratio of 3.7 obtained in the earlier model, which excluded lability; this implies that

the relation between mould and wheeze was largely unrelated to measurements of airways reactivity.

The higher prevalence of reported wheeze among children from homes with mould for any degree of airways reactivity suggested that reporting bias explained a substantial part of the association of wheeze with damp or mouldy housing. Bronchospasm after exercise (lability index <0.8) was, however, more common among the children from homes with mould. On the generous (but not unreasonable) assumption that all the children receiving drug treatment for asthma who were tested had reactive airways, the prevalence of abnormality was 9.9% (8/81) among children from homes with mould compared with 5.4% (43/792) among the remainder (table II). This difference was in the expected direction, although it did not reach significance ($\chi^2=1.90$, $df=1$). A non-parametric comparison of the entire distribution of lability in children from homes with and without mould was made using normal scores from the RANK procedure in SAS²² to correct for the pronounced skewness. The difference between the two groups was negligible (Student's $t=0.4$, $df=860$).

Discussion

This study confirms the finding of previous surveys in one part of Edinburgh and suggests that an association between damp or mouldy housing and respiratory symptoms is not confined to specific council estates or to rented as opposed to owner occupied housing.^{11,17} The association between mould and wheeze meets many of the criteria for an epidemiological association to be considered causal: it is strong, relatively specific when compared with other symptoms, consistent with previous studies, and free of substantial confounding by other factors studied.²³ Biologically plausible causal mechanisms can be proposed, and, assuming that duration of exposure is greatest when the child's bedroom is affected by mould or damp, there is a suggestion of a dose-response relation.

The association of wheeze with damp or mouldy housing was of particular interest not only because confounding by other features of the home environment was unlikely but also because a primary association with wheeze might account for the effect of damp, mouldy housing on other respiratory symptoms related to asthma. Furthermore, wheeze was the symptom for which a causal link with damp housing conditions was most plausible biologically.

The prevalence ratio for wheeze in the past year when homes with and without mould were compared is remarkable in view of the lack of correlation of most social or environmental variables with childhood asthma.²⁴ The study sample was drawn from the general population and permitted an estimate of the importance to public health of this association. If no child in the population of 1000 had been exposed to mould in the home 105 cases of wheeze during the past year would have been expected, based on 96 cases in 911 children (table I). As 123 cases were seen mould in the home accounted for 14% (18/123) of all cases of wheeze. This fraction of the population attributable risk varied with the prevalence of exposure, being 6% (4/5/75) for children from owner occupied homes but 26% (12/5/49) for children from rented homes. These proportions are certainly much greater than any corresponding hazards from cooking or heating fuels.

In a study of adults 43% of those living in areas of poor quality housing associated respiratory symptoms with their housing whereas in areas of good housing only 10% did so.²⁵ Differences such as this may reflect a causal relation, but they raise the possibility that reports of health state and particularly of respiratory symptoms may be influenced by perceptions of the

TABLE II—Prevalence (%) of wheeze in past year related to mould in home and bronchial lability induced by exercise. Numbers of children are given in parentheses

Lability index*	No mould	Mould in any room	Total
<0.8	48.6 (17/35)	60.0 (3/5)	50.0 (20/40)
0.8-0.99	11.1 (7/63)	44.4 (4/9)	15.3 (11/72)
0.9-0.99	8.9 (34/383)	33.3 (10/30)	10.7 (44/413)
≥1.0	6.4 (20/303)	14.7 (5/34)	7.4 (25/337)
Total	10.9 (86/792)†	30.9 (25/81)‡	12.7 (111/873)†‡

*Forced expiratory volume in one second after exercise divided by that before exercise.

†Includes eight children tested while receiving treatment, all of whom wheezed.

‡Includes three children tested while receiving treatment, all of whom wheezed.

home environment. The present study showed that at any given level of airways reactivity induced by exercise the prevalence of wheeze reported by parents of children from homes with mould was substantially higher than the prevalence reported for children from unaffected homes. Interpretation of these results depends on the validity of the exercise challenge as an objective indicator of respiratory disease.

Exercise was chosen because it is a common physiological challenge and therefore positive findings can be considered to have intrinsic validity. Pharmacological challenge tests may be more sensitive to minor degrees of airways reactivity, but they can induce bronchospasm in many non-wheezy children, which makes the interpretation of positive results less certain.²⁷ Although wheeze and bronchial lability were clearly related, in two thirds of the wheezy children the forced expiratory volume in one second after exercise was within 10% of the value determined before exercise. Any assessment of change in a spirometric index is sensitive to errors of measurement, particularly in this young age group. Repeating the measurements in the same population of children suggested that forced expiratory volume in one second was the most reproducible spirometric index, but its coefficient of variation within subjects on any given occasion was 8-5%; hence the lability index was subject to substantial random errors of measurement and individual subjects were misclassified.

Though lack of sensitivity and random errors in the test procedure may have reduced the power of the study to detect a true relation between reported mould and bronchial lability, the negative findings do not exclude an association. These limitations cannot, however, explain the different relations between wheeze and lability in the children from homes with and without mould. This difference could be explained if exposure to mould commonly resulted in a syndrome (or a subtype of asthma) that caused wheeze but was not associated with airways reactivity to exercise. By its very nature this is a difficult proposition to test objectively, but it is unlikely for two reasons. Firstly, epidemiological and clinical evidence supports the concept of childhood asthma as a single disease, the cardinal symptom of which is wheeze.^{27,28} Secondly, the most plausible causal mechanism for any association between mould and wheeze is allergy to airborne spores, but atopic skin reactions to common antigens are associated with more frequent wheeze,²⁹ and children who wheeze more frequently are more likely to show airways reactivity.³⁰

An alternative argument might be that bronchospasm induced by exercise reflects an underlying susceptibility to asthmatic attacks rather than the activity of the disease itself. In this case the prevalence of symptoms might depend on both host factors (non-specific bronchial hyperreactivity) and the "dose" of trigger factors in the environment (including mould spores). The results presented in table II could be interpreted as showing this, given that lability induced by exercise was an imprecise measure of underlying airways reactivity and that mould may not be a trigger for all susceptible children. Such a distinction between host and environmental factors is, however, called into question by observations that when patients with sensitivity to house dust mite move to an environment free of allergens the response of their bronchi to inhaled histamine is reduced.³¹ This suggests that non-specific bronchial hyperreactivity can result from long term exposure to allergen and is a manifestation of asthma rather than a cofactor in its aetiology.

The most straightforward explanation of the discrepancy between the questionnaire and clinical data is that awareness of dampness or mould in

the home is a determinant of parental reporting of symptoms; this would account for much of the observed association between mould and respiratory symptoms. The use of the term reporting bias should not be misunderstood. It does not mean that the accuracy of reporting by occupants of homes with mould is necessarily poorer; recall of symptoms for children in homes not affected by mould may be less complete. This reporting bias, however, implies that further studies of this relation are unlikely to be valid if they rely solely on information from questionnaires. An alternative source of reporting bias, which has not been considered here, is the effect of the child's symptoms on parental awareness of adverse conditions in the home. Ambient humidity and airborne fungal spores are being measured in subsamples of the study population to address this issue.

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SUMMARY: In 11 children with bronchial asthma (age range 8-13 yr, 10 boys, 1 girl) we studied the effect of an one hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham. Nine of the subjects were on regular therapy with inhaled B2-agonists and DSCG. Both components were withheld at least six hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations which caused a 100% increase in SRaw, PC100SRaw, and a 20% fall in FEV1, PC20FEV1. Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) cmH2O*s, mean FEV1(SD) was 1.97 (0.32) and 1.98 (0.40) l, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) cmH2O*s, mean FEV1 (SD) was 1.95 (0.37) and 1.94 (0.35) l, respectively. Geometric mean (SD) PC100SRaw and PC20FEV1 after Sham was 1.39 (3.0) and 0.70 (2.7) mg/ml, after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/ml respectively. There was no statistical difference in lung function and PC-values between Sham and passive cigarette smoking. The main symptoms during passive smoking were eye and nasopharyngeal irritation. Our observations suggest that in children with mild bronchial asthma one hour of passive cigarette smoking does not cause airway obstruction or changes in bronchial responsiveness.

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**ACUTE EFFECT OF PASSIVE SMOKING ON LUNG FUNCTION AND
AIRWAY RESPONSIVENESS IN ASTHMATIC CHILDREN ^a**

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Running title: Passive smoking in childhood asthma

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SUMMARY

In 11 children with bronchial asthma (age range 8-13 yr, 10 boys, 1 girl) we studied the effect of an one hour exposure at rest during passive cigarette smoking (20 ppm CO) or Sham. Nine of the subjects were on regular therapy with inhaled β_2 -agonists and DSCG. Both components were withheld at least six hours prior to each study session. Exposure was performed in an environmental chamber. Before and immediately after exposure, lung function and symptom scores were determined. After exposure, a histamine inhalation challenge was performed to determine the concentrations which caused a 100% increase in SRaw, PC₁₀₀SRaw, and a 20% fall in FEV₁, PC₂₀FEV₁. Mean (SD) SRaw before and after Sham was 8.7 (3.6) and 9.0 (3.2) cmH₂O*s, mean FEV₁ (SD) was 1.97 (0.32) and 1.98 (0.40) l, respectively. Before and after cigarette smoking, mean SRaw (SD) was 10.4 (5.3) and 9.4 (3.3) cmH₂O*s, mean FEV₁ (SD) was 1.95 (0.37) and 1.94 (0.35) l, respectively. Geometric mean (SD) PC₁₀₀SRaw and PC₂₀FEV₁ after Sham was 1.39 (3.0) and 0.70 (2.7) mg/ml, after passive smoking 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively. There was no statistical difference in lung function and PC-values between Sham and passive cigarette smoking. The main symptoms during passive smoking were eye and nasopharyngeal irritation. Our observations suggest that in children with mild bronchial asthma one hour of passive cigarette smoking does not cause airway obstruction or changes in bronchial responsiveness.

KEY WORDS:

Passive Smoking, Lung Function, Bronchial Hyperresponsiveness, Childhood Asthma

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INTRODUCTION

Subjects with bronchial asthma are characterized by airway hyper-responsiveness to a variety of stimuli. Cigarette smoke is considered to be a common stimulus which may affect subjects with asthma (1-3).

In children, the adverse effect of chronic passive smoking on respiratory symptoms has received increasing attention (4-7). In some of these investigations an association between parental smoking habits and acute lower respiratory illness (8-12), respiratory symptoms (13-16), prevalence and severity of asthma (13,17,18), impaired lung function and bronchial responsiveness (10,12,13,16,17,19-23) could be demonstrated.

In contrast to chronic exposure, little is known on the acute effect of passive smoking in children. We therefore studied symptoms, lung function and airway responsiveness of children with bronchial asthma before and after one hour exposure to cigarette smoke as compared to control conditions.

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MATERIAL AND METHODS

Patients

We investigated 11 children with allergic bronchial asthma (10 boys, 1 girl) ranging in age from 8 to 13 years (mean (SD) 10.4 (1.4) yr). Individual patient characteristics are given in table 1.

In all children the diagnosis of bronchial asthma was made up within at least 1 year before entering the study and patients had been followed up for a longer period of time on an out-patient basis. The children were not selected on the basis of symptoms induced by cigarette smoke.

Diagnosis was based on typical symptoms, reversible airflow obstruction, bronchial hyperresponsiveness to histamine and a positive prick skin test to at least one common allergen (Allergopharma, Reinbek, FRG). Six out of 11 patients showed an increase in total IgE (>150 IE/ml), and 6 children an increase of eosinophils in peripheral blood ($>300/\text{mm}^3$).

In all subjects the severity of asthma required a long-term therapy, which had to be continued in 9 of 11 children during the study period. All children on therapy received disodium cromoglycate, two puffs two to four times per day. Each puff of disodium cromoglycate (1 mg) was combined with 0.05 mg fenoterol (Ditec^R) or 0.5 mg reproterol (Aarane^R) as a β_2 -agonist. One subject took two additional puffs of 200 μg beclomethasone dipropionate. In all children, this therapeutic regime was sufficient to control the disease and allow normal activities. This is also reflected by the magnitude of morning (before therapy, PEF_{min}) and maximum daytime peak flow values (PEF_{max}), which were measured regularly (table 1).

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In the 9 asthmatic children receiving regular therapy, the activity of the disease allowed to discontinue inhalation therapy at least six hours prior to each study session without precipitating symptoms or deteriorating lung function (subject 6 continued beclomethasone inhalation during the study period).

Spirometry, measured at least six hours after inhaling a bronchodilator was within normal limits. In all children the provocative concentration of inhaled histamine necessary to decrease FEV₁ by 20% as compared to baseline was less than 8 mg/ml (table 1), thus demonstrating airway hyperresponsiveness (see Histamine inhalation challenge).

During the study period and within the two weeks preceeding the study no child suffered from an upper respiratory tract infection, experienced an uncommon burden of allergen or reported on any other trigger which may worsen asthma; therefore all included children were considered to be currently clinically stable.

None of the children had ever actively smoked cigarettes, six of them were exposed to cigarette smoke at home (table 2).

Children and parents were informed about the aim of the study and gave their consent.

Cigarette smoke exposure

Exposure chamber

The study was performed in a 24 m³ exposure chamber. To ensure homogenous concentration of cigarette smoke the air was moved by fans in

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a spiral form. Sampling ports were distributed within the chamber to check for gradients of gas concentrations and particle density. Cigarette smoke was generated by a smoking machine designed in our laboratory which took 1 puff per cigarette per minute (according to DIN 10240). To achieve the target concentration of about 20 ppm CO, on average 2 cigarettes were smoked simultaneously. We used filter cigarettes of a leading brand with a nicotine content of 0.9 mg and tar content of 13 mg per cigarette.

Measurement of exposure conditions

The level of cigarette smoke exposure was determined by measuring CO, NO_x, particle density, nicotine, acetaldehyde, formaldehyde, acrolein and ammonia. Concentration of CO was measured continuously by an infrared gas analyzer (Unor 6N, Maihak AG, Hamburg, FRG) whose calibration was checked daily by a certified span gas (Linde AG, Unterschleißheim, FRG). Concentration of NO_x was measured by a chemiluminescence nitrogen oxides analyzer (8840, Monitor Labs Inc., San Diego, CA, USA) which was calibrated regularly by a permeation tube calibrator (Model 8550, Monitor Labs Inc., San Diego, CA). Particle density was monitored continuously by measuring optical particle density (RAM-1, GCA/Environmental Instruments, Bedford, Mass., USA) using a 4 µm precollector. Calibration of optical particle density was done in regular intervals gravimetrically by taking filter probes (Millipore, FALP 03700, Typ FA) from total sampling volumes of 17-73 litres of air. Nicotine, acetaldehyde, formaldehyde, acrolein and ammonia were determined using commercially available sample tubes and filters at sampling volumes ranging between 3 and 100 litres of air. Analysis was done by gas chromatography (nicotine), by high performance

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liquid chromatography (acetaldehyde, formaldehyde, acrolein) and by the indophenol method VDI 2461 (ammonia). Temperature and relative humidity were measured at the beginning and at the end of each exposure.

Estimation of chronic smoke exposure

To estimate chronic passive smoke exposure at home, urinary cotinine concentrations were determined in triplicate from morning urine specimens collected at the second study day. Determination was made in an environment free of smoking. Urine was stored at -20 °C until assayed. Cotinine was measured by a radioimmunoassay procedure (24).

Assessment of symptoms

Before and immediately after exposure the chest of each subject was auscultated by one of us (M.O.). To estimate severity of symptoms induced by exposure, the children and their parents were instructed to check an ordinal scale ranging from 0 to 10 in order to determine severity of eye, nose irritation, throat irritation, cough, chest tightness and headache. Zero indicated no perceptible symptom, 10 almost intolerable severity of the respective symptom.

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Lung Function Measurement

Airway resistance (R_{aw}) during breathing at 1 Hz and thoracic gas volume (TGV) were measured by a volume-constant body plethysmograph (Bodytest, E. Jaeger, Würzburg, FRG) connected to a Computer (PDP 11/04, Digital Equipment Corp., Maynard, MA, USA). Airway resistance was multiplied by the corresponding thoracic gas volume to obtain specific airway resistance (S_{Raw}). Airway resistance was measured during up to 4 breathing cycles. FEV_1 was assessed by a pneumotachygraph immediately after body plethysmography. Measurements were repeated 4 times. For analysis, the average of 4 values of S_{Raw} and the average of the two maximum values of FEV_1 was taken.

Histamine Inhalation Challenge

Bronchial challenge with histamine was done according to the guidelines of Chai et al. (25) using a breath-synchronized pressure valve. The aerosols were generated during 0.6 sec. at the beginning of 5 slow inspirations from FRC to TLC, the nebulizer output being 80 μ l of solution per 5 nebulizations. Saline solutions of histamine diphosphate (Sigma Chemie, Deisenhofen, FRG) were prepared daily. After inhaling buffer solution, the subjects inhaled doubling concentrations of histamine, starting with 0.05 mg/ml histamine. Lung function was measured 1 and 3 min after inhalation. The inhalation was stopped after at least a 100 % increase of S_{Raw} and a 20 % fall in FEV_1 . Dose-response curves were constructed by plotting S_{Raw} and FEV_1 against log histamine concentration. By linear interpolation, the provocative

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concentrations of histamine (in mg/ml) were computed necessary to increase SRaw by 100 % ($PC_{100}SRaw$) and to decrease FEV_1 by 20 % ($PC_{20}FEV_1$) as compared to baseline. With this method, hyperresponsiveness was assumed if PC-values were below 8 mg/ml (26).

Experimental Protocol

Each subject was studied at three days within a two week period. All investigations were performed at least six hours after the last application of therapy.

On the first day recent history was taken and a physical investigation performed. Lung function and airway responsiveness to inhaled histamine were measured. In case of stable clinical conditions, normal lung function and airway hyperresponsiveness, the children and their parents were instructed in the experimental procedure. They were provided with sampling probes for collecting morning urinary specimens.

On the second study day, exposure to ambient air (Sham) and at the third study day exposure to cigarette smoke was performed.

On exposure days, subjects rested for 10 minutes after entering the laboratory. After auscultation of the chest, assessment of symptoms and measurement of baseline lung function, the children entered the exposure chamber. They were always seated at the same place inside the chamber. Five minutes before the end of exposure, symptoms were assessed again. Immediately after exposure, auscultation of the chest and lung function measurement were performed. Histamine inhalation challenge was started 15 minutes after the end of exposure.

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Statistical Analysis

Lung function parameters before and after both exposures and control values were compared to each other by the paired t-test after appropriate Bonferroni correction for multiplicity of tests (27). Log PC-values after both exposures and control values were also compared by the paired t-test. The assumption of normal distribution of data was checked by normal probability plots and tests. Statistical significance was assumed for $p < 0.05$.

RESULTS

Exposure conditions

During Sham and cigarette smoke exposure, mean (SD) temperature was 24.1 (1.6) °C and mean relative humidity was 51 (3) %, with no difference between the study days. During passive smoke exposure, mean (SD) total particle density was 2743 (348) $\mu\text{g}/\text{m}^3$ and nicotine content was 397 (78) $\mu\text{g}/\text{m}^3$. Mean (SD) concentrations of CO were 20.5 (0.5) ppm, NO_x 0.90 (0.09) ppm, formaldehyde 0.13 (0.01) ppm, acetaldehyde 0.50 (0.05) ppm, acrolein 0.081 (0.017) ppm and ammonia 5.69 (3.35) ppm. During exposure with ambient air, mean (SD) CO was 0.1 (0.3) ppm, and mean (SD) total particle density was 17 (57) $\mu\text{g}/\text{m}^3$.

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Symptoms during exposure

In all of our children, auscultation of the chest was normal before and after exposure to Sham and cigarette smoke, respectively. Eye irritation was experienced by all subjects during smoke exposure (Fig. 1). Nasal congestion was reported by 9/11 children after cigarette exposure and 5/11 after Sham. After smoke exposure, throat irritation occurred in 3/11, cough in 0/11, chest tightness in 3/11, and headache in 3/11 children. Except for eye irritation, the frequency and intensity of the symptoms did not differ between cigarette smoke and Sham exposure (Fig. 1).

Variability of baseline lung function

Mean (SD) SRaw before Sham and smoke exposure was 8.7 (3.6) and 10.4 (5.3) cmH₂O*s, respectively. These values were not significantly different from each other nor from the mean (SD) SRaw value of 8.5 (2.8) cmH₂O*s measured on study entry (control, table 3).

Mean (SD) FEV₁ before Sham and cigarette smoke was 1.97 (0.32) and 1.95 (0.39) l, respectively. These values were not significantly different from each other nor from the mean (SD) FEV₁ value of 1.95 (0.39) l when entering the study (control, table 3).

Mean (SD) values of individual variation coefficients of the three repeated determinations of SRaw and FEV₁ were 21 (11) and 6 (4) %, respectively.

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Lung function changes during exposure

Mean (SD) SRaw before and after one hour exposure to ambient air (Sham) was 8.7 (3.6) and 9.0 (3.2) cmH₂O*s, respectively, with no statistically significant difference (table 3). Mean (SD) FEV₁ before and after Sham was 1.97 (0.32) and 1.98 (0.40) l, respectively, with no significant difference. Percentage changes of SRaw and FEV₁ during Sham ranged from -28 to +59% and from -10 to +9%, respectively.

Mean (SD) SRaw before and after one hour exposure to cigarette smoke was 10.4 (5.3) and 9.4 (3.3) cmH₂O*s, respectively. Mean (SD) FEV₁ before and after smoke exposure was 1.95 (0.39) and 1.94 (0.35) l, respectively (table 3, Fig. 2). Values before and after exposure were not significantly different from each other. Percentage changes of SRaw and FEV₁ during passive smoking ranged from -37 to +12% and from -25 to +13%, respectively.

Airway responsiveness during exposure

Geometric mean (SD) PC₁₀₀SRaw and PC₂₀FEV₁ at control were 0.85 (2.4) and 0.54 (2.7) mg/ml, respectively (table 4, Fig. 3).

Geometric mean (SD) PC₁₀₀SRaw and PC₂₀FEV₁ measured after Sham were 1.39 (3.0) and 0.70 (2.7) mg/ml, respectively. Geometric mean (SD) PC₁₀₀SRaw and PC₂₀FEV₁ after exposure to cigarette smoke were 1.65 (2.5) and 0.96 (2.3) mg/ml, respectively (table 4, Fig. 3).

PC₁₀₀SRaw and PC₂₀FEV₁ were not significantly different between Sham, cigarette smoke exposure or control.

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As determined from Sham and control, the mean (SD) value of individual variability of $PC_{100}SRaw$ and $PC_{20}FEV_1$ was 1.0 (0.5) and 0.9 (0.6) doubling concentrations of histamine, respectively.

DISCUSSION

Our observations demonstrate that in children with mild bronchial asthma one hour passive smoking produced mainly eye irritation but no airway obstruction and no significant changes in bronchial responsiveness to inhaled histamine.

To the best of our knowledge, acute pulmonary response to passive smoke exposure has not been studied in asthmatic children. Previous studies on the acute effect of passive smoking were performed in adult asthmatics. These studies showed conflicting results.

Shephard and coworkers (28) investigated 14 asthmatic subjects during a 2-h cigarette smoke exposure (24 ppm CO) and observed no significant changes in pulmonary function. Dahms et al. (29) reported on 10 asthmatics passively exposed to cigarette smoke (15 - 20 ppm CO) for one hour. These authors found a 21.4% decrease in FEV_1 following smoke exposure in asthmatics compared to normal controls. Knight and Breslin (30) studied 6 patients with asthma who developed a 11% decline in FEV_1 and an increase in bronchial reactivity to inhaled histamine 4 hours after a 1-h smoke exposure (15 - 25 ppm CO). Wiedemann and coworkers (31) examined the acute effect of a 1-h chamber exposure to cigarette smoke (40 - 50 ppm CO) on lung function and airway responsiveness in 9 adult asthmatics. In these subjects no change in lung function was observed, but a small decrease in nonspecific airway

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reactivity. Recently, Stankus et al. (32) investigated the effect of an 2 hour exposure to tobacco smoke (8.7 - 14.1 ppm CO) in 21 subjects with asthma who claimed on respiratory symptoms on previous exposure to cigarette smoke. In 7 of these 21 subjects suspected as smoke sensitive asthmatics, they found a significant ($> 20\%$) fall in FEV_1 . These findings in adult asthmatics demonstrate that there might be a subgroup of smoke sensitive asthmatics who develop acute airway obstruction without consistent changes in airway responsiveness following passive smoke exposure.

In our group of asthmatic children, after exposure to Sham changes of FEV_1 between -10 and +9% were observed as compared to pre-exposure values. After exposure to passive cigarette smoke, in 9 subjects changes of FEV_1 were within this range. Subject #3 showed an increase in FEV_1 by 13% after smoke exposure in contrast to an decrease of 10% after Sham. Subject #7 showed a decrease in FEV_1 by 25% after smoke exposure as compared to an increase of 5% after Sham. In both subjects, changes in FEV_1 were larger than corresponding changes in $SRaw$. Analysis of the spirometric curves, however, did not reveal any sign of deficient cooperation in both subjects. According to our study protocol, baseline lung function measurement was performed three times on three different study days. Mean coefficients of variation were 6% for FEV_1 and 21% for $SRaw$ which is well within the reproducibility reported in adult subjects (33). Therefore, we do not believe that our inability to demonstrate an adverse acute effect of passive cigarette smoking on lung function was due to an insufficient reproducibility of lung function data.

Airway hyperresponsiveness to inhaled histamine in terms of $PC_{20}FEV_1$ and $PC_{100}SRaw$ was assessed three times on three different study days. The two challenges without previous smoke exposure (control, Sham) showed a variability of plus minus one doubling concentration of histamine, which is

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within accepted limits (33,34). Therefore, it is unlikely that our findings were due to a weak reproducibility of bronchial responsiveness measurement. However, it seems to us that in children further investigations on the possible interaction between DSCG and passive smoking should be done.

Nine out of 11 asthmatic children were under regular therapy consisting of inhaled β_2 -agonists and disodium cromoglycate (and in subject #6 of additive 400 μ g beclomethasone dipropionate). The duration of the effect of inhaled β_2 -agonists on airway tone and bronchial responsiveness is within 3 - 5 hours (35). Therefore, as we started exposure at least 6 hours after the last inhalation therapy, an influence of β_2 -agonists on our data seems to be unlikely.

This may however not be true for disodium cromoglycate (DSCG). There are conflicting data on the protective effect of DSCG on airway responsiveness. Most authors agree that a significant protection against airway obstruction induced by histamine or methacholine could not be substantiated (36). Recently it has been shown that long term treatment with DSCG may modify the level of bronchial hyperresponsiveness (37).

In our study all children showed bronchial hyperresponsiveness to inhaled histamine, irrespective of the foregoing therapy with DSCG. Three of the 9 children with DSCG showed an increase in airway responsiveness after passive cigarette smoking, the remaining children an decrease in airway responsiveness. In comparison, one child without therapy showed an increase and the other one without therapy showed a decrease in hyperresponsiveness after smoke exposure. Our inability to demonstrate an effect of passive smoke exposure on airway responsiveness in the presence of hyperresponsiveness to inhaled histamine is unlikely to be explained by the pharmacologic profile of DSCG.

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In the present study the level of cigarette smoke exposure was characterized by several components which may be potential irritants per se. It has been suggested that substances like CO (38), NO₂ (39), formaldehyde (40) and aerosolized nicotine (41) may produce upper respiratory symptoms. The threshold concentration of NO₂ which causes an increase in hyper-responsiveness during resting ventilation is about 0.25 ppm (39). In our experiments, total NO_x concentration was about 1 ppm, however, the reactive component NO₂ was measured to be less than 3% of the total concentration of NO_x. Acrolein (an unsaturated aldehyde) has been demonstrated to decrease pulmonary function in guinea pigs at concentrations of at least 0.31 ppm and to produce transient bronchial hyperresponsiveness (42,43). In our study the concentration of acrolein was in the range of 0.1 ppm. For saturated aldehydes like formaldehyde it has been reported that in asthmatics exposure to concentrations up to 3 ppm for 1 - 1.5 hour did not cause statistically significant decrements in pulmonary function (40,44). Under our exposure conditions, formaldehyde concentration was about 0.13 ppm. Therefore, our concentrations of the cigarette smoke components were always lower than those effective in the single component exposure studies. Because we did not see an effect of passive smoking on lung function or airway responsiveness, synergistic effects between the constituents of cigarette smoke seems to be unlikely.

By measuring urinary cotinine concentration which is an accepted biological marker of chronic exposure to passive smoke (45-48), we were able to identify 6 out of 11 asthmatic children with reported passive smoke exposure at home (table 2). This observation confirms that many children are exposed by the smoking habits of their parents. Since the purpose of our study was to investigate the acute effects of passive smoking and since we did not find an

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effect and could not identify an active component of cigarette smoke in our experiments, it is difficult to compare our data with those of chronic exposure studies. Chronic exposure has been demonstrated to increase bronchial responsiveness and to impair lung function (10,12,13,16,17,19-23). Our data regarding short-term exposure are by no means contradictory to these observations. In addition, chronic passive smoke exposure may induce changes in the airways which mask airway response to acute exposure. From our data this hypothesis can not be proved, however, it would be of interest to study the acute airway response of asthmatic children with and without chronic smoke exposure.

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LEGENDS TO FIGURES

- Figure 1 Median and 90%-percentil of symptom score after Sham and passive smoke exposure.
- Figure 2 FEV₁ (l) and SRaw (cmH₂O.s) before and after exposure (Sham, Passive Smoking) and at the control day.
- Figure 3 Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

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Legend to Table 1:

^aVC: Inspired vital capacity.

^bGeometric mean values and geometric standard deviations of mean.

^cTherapy: B = inhaled beta-2-agonists, D = disodium cromoglycate, CI = Inhaled corticosteroids.

For definitions see text.

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TABLE 1 - Individual data of patients

Patient No.	Sex	Age yr	Weight kg	Height cm	Atopy	IgE IE/ml	Eosinophils counts/mm ³	PEF _{min} l/min	PEF _{max} l/min	VC ^a lBTPS	FEV ₁ %pred	PC ₂₀ FEV ₁ ^b mg/ml	Therapy ^c
1	m	12	50	165	+	92	563	400	480	3.68	97	0.09	B,D
2	m	13	42	154	+	114	350	280	330	2.18	76	0.34	B,D
3	m	11	35	142	+	524	422	320	440	2.35	97	0.73	B,D
4	m	9	38	140	+	219	100	300	380	2.46	110	1.25	B,D
5	m	10	35	150	+	518	441	280	340	2.48	88	1.72	B,D
6	m	11	40	149	+	146	319	300	380	2.60	111	1.02	B,D,iC
7	m	11	41	151	+	101	181	330	400	2.60	107	1.13	B,D
8	m	9	40	141	+	269	143	240	270	1.90	85	0.12	B,D
9	m	8	26	137	+	137	147	210	330	1.82	90	1.28	-
10	m	10	36	142	+	361	422	280	350	3.00	130	0.46	B,D
11	w	10	35	143	+	185	293	150	220	2.20	98	0.30	-
Mean		10.4	38	147		242	307	281	356	2.48	99	0.77	
SD		1.4	6	8		159	149	65	73	0.52	15	0.55	

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TABLE 2 - Urinary cotinine concentration and reported parental smoking habits

Patient No.	cotinine (ng/ml)	paternal smoking	maternal smoking
1	11	+	-
2	8	+	-
3	34	-	-
4	4	+	-
5	2	-	-
6	1	-	+
7	3	-	+
8	0	-	-
9	11	+	-
10	0	-	-
11	0	-	-

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TABLE 3 - SRaw (in cmH₂O-s) and FEV₁ (in l) before (pre) and after (post) exposure to ambient air (Sham) or passive smoke and at the control day

Patient No.	CONTROL		SHAM				PASSIVE SMOKE			
	SRaw	FEV ₁	SRaw		FEV ₁		SRaw		FEV ₁	
			pre	post	pre	post	pre	post	pre	post
1	13.2	2.68	12.5	10.6	2.60	2.84	9.9	11.1	2.76	2.81
2	8.1	1.74	5.9	7.9	1.93	1.86	8.6	9.4	1.84	1.82
3	10.7	1.75	12.6	12.8	1.75	1.57	9.6	8.8	1.74	1.97
4	10.1	1.90	4.6	7.3	2.13	2.11	11.1	9.3	1.83	1.84
5	10.5	1.86	11.9	12.7	1.71	1.75	14.3	14.0	1.47	1.55
6	8.1	2.30	9.0	7.8	2.27	2.32	10.5	8.8	2.23	2.26
7	5.2	2.28	5.8	4.2	2.21	2.33	4.6	4.4	2.33	1.74
8	4.0	1.52	6.6	7.2	1.76	1.75	6.4	6.2	1.79	1.78
9	5.4	1.47	3.5	4.4	1.82	1.69	5.5	5.4	1.59	1.72
10	10.8	2.33	13.9	13.0	2.07	2.10	23.9	15.0	2.21	2.13
11	7.8	1.64	9.7	10.6	1.47	1.50	9.7	10.6	1.63	1.71
Mean	8.5	1.95	8.7	9.0	1.97	1.98	10.4	9.4	1.95	1.94
SD	2.8	0.39	3.6	3.2	0.32	0.40	5.3	3.3	0.39	0.35

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Legend to Table 4:

^aGeometric mean values and geometric standard deviations of mean.

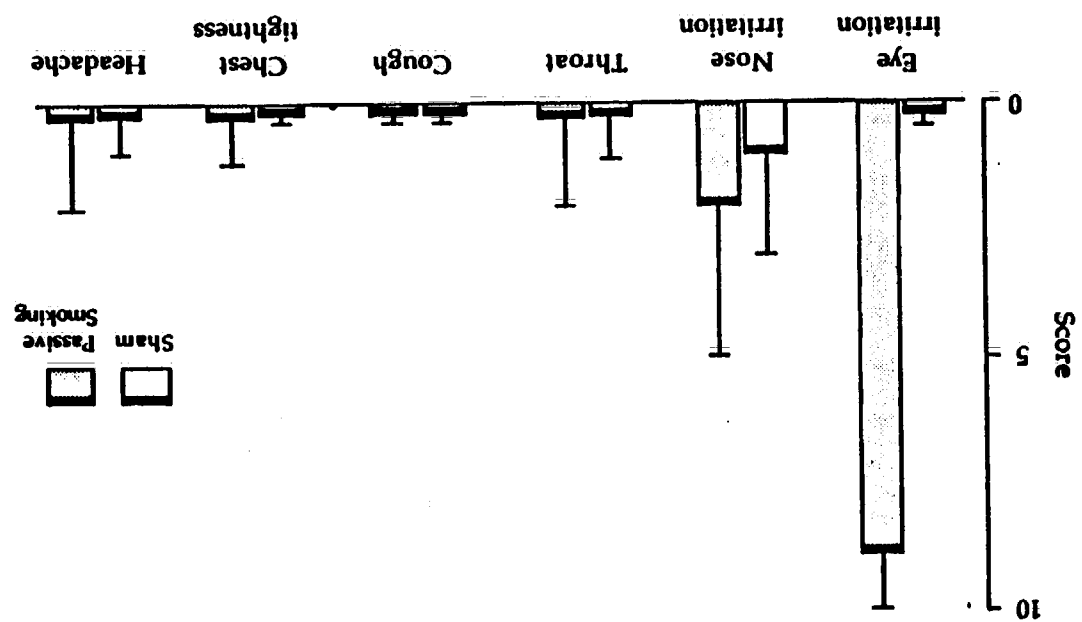
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TABLE 4 - Histamine concentration (mg/ml) necessary to increase SRaw by 100% (PC₁₀₀SRaw) or to decrease FEV₁ by 20% (PC₂₀FEV₁) after 1 hour exposure to ambient air (Sham) or to passive smoke and at the control day

Patient No.	<u>CONTROL</u>		<u>SHAM</u>		<u>PASSIVE SMOKE</u>	
	PC ₁₀₀ SRaw	PC ₂₀ FEV ₁	PC ₁₀₀ SRaw	PC ₂₀ FEV ₁	PC ₁₀₀ SRaw	PC ₂₀ FEV ₁
1	0.25	0.09	0.51	0.27	0.30	0.21
2	0.92	0.34	5.81	0.78	6.40	1.10
3	1.60	0.73	0.38	0.11	1.24	1.05
4	1.12	1.25	2.38	0.79	1.17	0.87
5	1.45	1.72	4.59	1.68	3.16	2.64
6	2.12	1.02	3.83	1.71	6.90	3.03
7	1.07	1.13	0.59	0.60	1.45	1.57
8	0.12	0.12	0.62	0.67	1.01	1.14
9	1.85	1.28	4.80	4.22	1.40	0.75
10	0.81	0.46	0.37	0.33	0.70	0.27
11	0.66	0.30	1.24	0.68	2.79	1.00
Mean ^a	0.85	0.54	1.39	0.70	1.65	0.96
SD	2.40	2.70	3.00	2.70	2.50	2.30

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Fig. 1. Median and 90%-percentile of symptom score after Sham and passive smoke exposure.



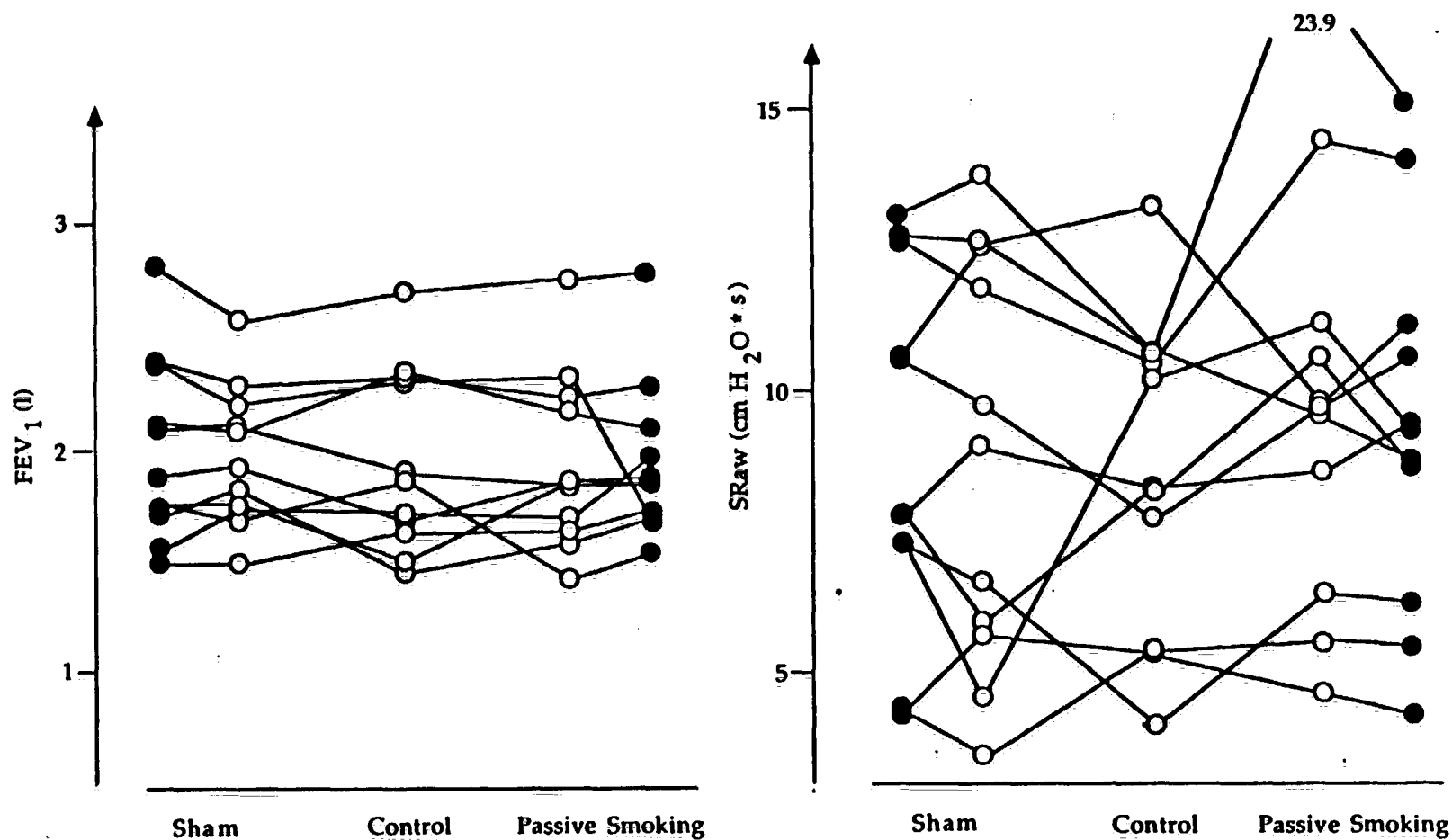


Fig.2. FEV₁ (l) and SRaw (cmH₂O*s) before (O) and after (●) exposure (Sham, Passive Smoking) and at the control day (O).

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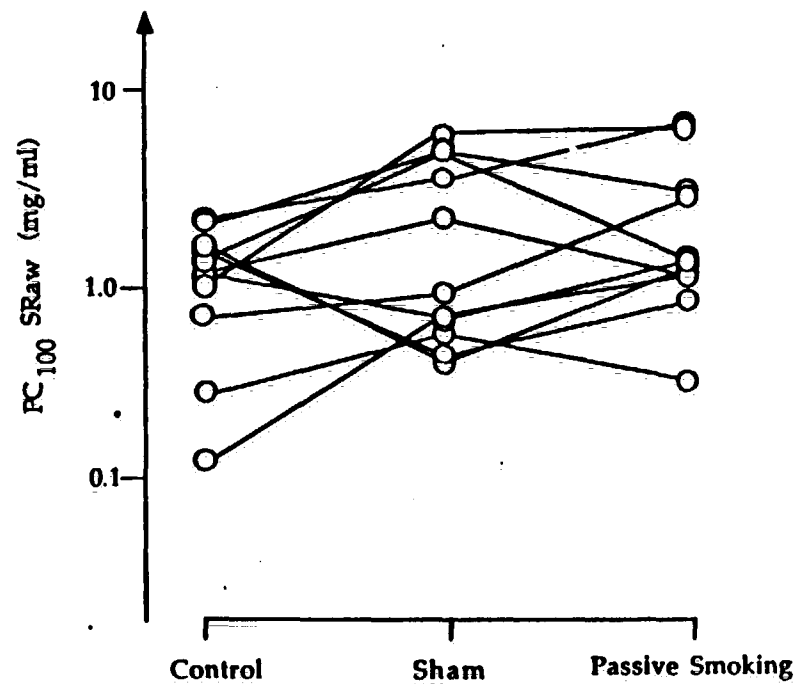
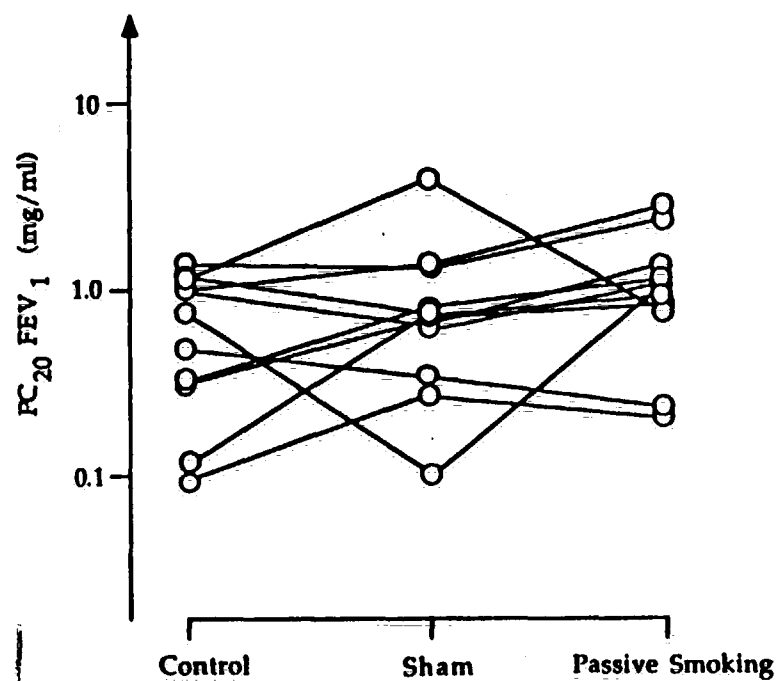


Fig. 3. Airway responsiveness to inhaled histamine after exposure (Sham, Passive Smoking) and at the control day.

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Sherman, C.B., Tosteson, T.D., Tager, I.B., Speizer, F.E., Weiss, S.T. "Early childhood predictors of asthma" Am J Epidemiol 132(1): 83-95, 1990.

ABSTRACT. To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5-9 years from East Boston, Massachusetts, that has been under study since 1975. The disease outcome considered was age at first onset of asthma, as determined by parental or self-reporting of a physician's diagnosis. Potential risk factors were evaluated specifically in relation to their presence antecedent to a diagnosis of asthma. Standardized questionnaires were used to obtain childhood illness histories, environmental exposures, and the asthmatic and atopic statuses of first-degree relatives. Ninety-one cases of asthma were identified from 1975 to 1988 (57 males and 34 females). Significant sex-adjusted relative risk estimates were seen for antecedent pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma. A history of parental asthma or parental atopy did not significantly alter the sex-adjusted relative risk estimates for pneumonia, bronchitis, hay fever, or sinusitis. These results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences.

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EARLY CHILDHOOD PREDICTORS OF ASTHMA

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Sherman, C. B. (Pulmonary Div., The Miriam Hospital, Providence, RI 02906), T. D. Tosteson, I. B. Tager, F. E. Speizer, and S. T. Weiss. Early childhood predictors of asthma. *Am J Epidemiol* 1990;132:83-95.

To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5-9 years from East Boston, Massachusetts, that has been under study since 1975. The disease outcome considered was age at first onset of asthma, as determined by parental or self-reporting of a physician's diagnosis. Potential risk factors were evaluated specifically in relation to their presence antecedent to a diagnosis of asthma. Standardized questionnaires were used to obtain childhood illness histories, environmental exposures, and the asthmatic and atopic statuses of first-degree relatives. Ninety-one cases of asthma were identified from 1975 to 1988 (57 males and 34 females). Significant sex-adjusted relative risk estimates were seen for antecedent pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma. A history of parental asthma or parental atopy did not significantly alter the sex-adjusted relative risk estimates for pneumonia, bronchitis, hay fever, or sinusitis. These results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences.

asthma; child; genetics; hypersensitivity; respiratory tract infections

A number of studies have been carried out to investigate risk factors for childhood asthma (1-16). Hospital-based and case-control studies have consistently shown that lower respiratory illness (1-6) and atopy (7-10) are associated with asthma in children. Available longitudinal and community-based studies have found asso-

ciations between perinatal, social, infectious, and allergic exposures and the risk of asthma in children (11-16). Some uncertainty remains, however, as to the identity and causal significance of early childhood predictors for the development of asthma. The present investigation used longitudinal data from a cohort of 5- to 9-year-old chil-

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Abbreviations: FEF₂₅₋₇₅, forced expiratory flow from 25 percent to 75 percent of forced vital capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

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dren with 13 years of follow-up to evaluate the importance of a range of potential risk factors whose assessment was made antecedent to the onset of asthma.

MATERIALS AND METHODS

Selection of study sample

Details of the characteristics of the study population have been published elsewhere (17). Briefly, a 34 percent random sample was selected from all children 5-9 years of age enrolled in public and parochial schools in East Boston, Massachusetts, in September 1974. Between January and June of 1975, interviewers visited the households of these children and enumerated all household residents. The residents together with the index children comprised the total study population. All members of the study population were screened annually beginning in 1975, with the exception of the second and third screenings (1976 and 1977). The 5- to 9-year-old index children and siblings of the same ages comprised the study population for these analyses. Data collected during the first year (1975) and for 11 consecutive years (1978-1988) were used.

Data collection

Standardized questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history, and household demographics. Questions relating to chronic respiratory symptoms were those proposed by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (18). At the first screening, separate but similar questionnaires were used for subjects aged less than 10 years and those aged 10 years or older. Beginning with the fourth screening cycle (September 1977-June 1978), a common questionnaire was used for all subjects. Parents answered all questions for children younger than 10 years of age, except for those questions that pertained to the child's smoking history,

which were answered by the child during pulmonary function testing (when parents were not present). Children aged 10 or older answered all questions for themselves.

The time periods covered by these questionnaires differed. The initial questionnaire asked about events in the child's life prior to and up to entry into the study; the fourth year questionnaire focused on events for the period between study entry and the fourth year ("gap" years). Thereafter, each annual survey obtained information about events that occurred between annual surveys or between the time the subject was last seen and the current survey. The age at first occurrence of an illness was defined as the age (in years) at the time of the survey in which a positive response was recorded or the age (in years) at the time of the fourth survey for positive responses occurring during the "gap" years.

Ventilatory function was tested using an 8-liter, water-filled, portable recording spirometer (Survey spirometer; Warren Collins, Inc., Braintree, MA) with the subject in the sitting position and without the use of a nose clip. The spirometers were calibrated on a regular basis. Subjects were encouraged to perform FVC maneuvers until five acceptable tracings were obtained or until it became evident that they could not perform adequately. A tracing was considered acceptable if it was at least 4 seconds in duration and reached an asymptote of at least 1 second. All pulmonary function measurements were corrected to body temperature, ambient pressure, and saturation with water vapor at these conditions.

FVC, FEV₁, and FEF₂₅₋₇₅ were obtained by standard technique (19). FVC, the greatest volume that can be forcefully exhaled from total lung expansion, may be reduced in subjects with restrictive or severe obstructive ventilatory defects. FEV₁ and FEF₂₅₋₇₅, measures of airflow, are reduced in obstructive lung diseases. When mean values of these measurements were used, they were obtained as the mean of the best three of five tracings, as recommended by

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the Division of Lung Diseases (18). Mean lung function values were converted into percent predicted values using the nomograms of Dickman et al. (20).

The disease outcome for this investigation was age at first occurrence of a physician's diagnosis of asthma, as reported by the subject or his/her parent. Hay fever, sinusitis, eczema, pneumonia, and bronchitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial or yearly surveys. Smoking statuses of the index children and their parents were determined from the initial or yearly questionnaire responses. Croup and bronchiolitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial questionnaire. Age at first occurrence was obtained for these latter variables.

Other exposure variables included delivery complications, parental asthma, and parental atopy. Information on delivery complications ("Were there any problems with him/her at the time of delivery?"—yes or no) was available only on the initial questionnaire. A parental history of asthma was considered present if either parent of the index child reported, at any time during the study period, ever receiving a physician's diagnosis of the condition. Similarly, parental atopy was defined as self-reporting by either parent of a physician's diagnosis of hay fever and/or eczema at any time during the study period.

Follow-up and losses to follow-up

Asthmatics and nonasthmatics were followed for a comparable number of years (9.2 ± 3.0 (standard deviation) vs. 8.9 ± 3.5 , respectively; $p = 0.44$). No sex differences in follow-up years were detected. Incident asthmatics, however, were followed for significantly more years than nonasthmatics (9.7 ± 2.5 vs. 8.9 ± 3.5 , respectively; $p = 0.04$), possibly reflecting greater personal or parental concern about their illness.

Of the original 770 members of the cohort, 86 (11.2 percent) were lost to follow-up after the initial survey. At the initial survey, 81 of these subjects were identified as nonasthmatic (11.9 percent of 679 never asthmatics) and five subjects were identified as asthmatic (5.5 percent of 91 asthmatics).

Statistical analysis

The overall goal of the analysis was to identify risk factors for the onset of asthma, whose occurrence antedated the time ("age") of first diagnosis of asthma. The Cox proportional hazards model with time-dependent covariates and age as the time variable was used for this purpose (21).

This method was selected because it 1) accounts for the variable length of follow-up time available for each subject and 2) permits the use of covariate data that can legitimately change from survey to survey. The second feature was used in the following way to evaluate the relative risk of first onset of asthma: For those childhood illnesses for which age at first occurrence was available, an age-dependent covariate was created with a value of 1 (exposed) for ages greater than the age at first occurrence of the illness and 0 (unexposed) for ages less than or equal to the age at first occurrence of illness. The procedure assured that any observed increase in risk must pertain to antecedent occurrence of the illness. For comparative purposes, a second age-dependent covariate was created with a value of 1 (exposed) for ages greater than or equal to the age at first occurrence of the illness. The observed increase in risk using this covariate pertained to an antecedent or concurrent exposure.

The application of the Cox model required determining the age of first onset of asthma, as well as the age of first occurrence of other childhood respiratory illnesses. These determinations were complicated somewhat by the pattern of administration of the questionnaire. In the first

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year of the study, information concerning age of onset was requested whenever an occurrence of illness was reported. Thus, for ages of onset prior to entry into the study, there is a potential recall bias. This was investigated by introducing an age-dependent variable with a value of 1 for ages of onset at or following entry into the study and 0 for ages before entry, and by fitting interaction effects between this variable and the covariates of interest.

The questionnaire administered in the fourth year of the study did not request the age of onset for asthma and other illnesses occurring since the first year of the study. For illnesses occurring in this 2-year "gap," the age of onset was taken to be the age of the child at year 4 of the study. To examine the impact of this procedure, we performed analyses using 1) the age at year 1 of the study for both the covariate illnesses and asthma; 2) the age at year 1 of the study for the covariate illness with the age at year 4 for asthma; and 3) the reverse of the assignments in part 2.

Student's *t* tests (two-tailed) were used for comparison of mean spirometric values for asthmatics and nonasthmatics. Only the most recent spirometric lung function for each individual was used in the analysis. Chi-square statistics and Fisher's exact test (two-tailed) were used to test for associations between sex and use of medications and hospitalizations for asthmatics.

RESULTS

Characteristics of asthmatics

There were 91 subjects diagnosed as having asthma during the 13 years of the study. Forty-three asthmatics were diagnosed after entry into the study. Male asthmatics exceeded the expected number based on the sex distribution of the study population (asthmatics: 57 (62.6 percent) males and 34 (37.4 percent) females; study population: 402 (52.2 percent) males and 368 (47.8 percent) females; $p < 0.05$).

Asthmatics and nonasthmatics had nor-

mal ranges for all spirometric tests analyzed. All of these spirometric comparisons were performed using the most recently available spirometric lung function values for all individuals. Male asthmatics had larger FVC percent predicted values than male nonasthmatics (102.2 ± 1.7 (standard error of the mean) vs. 98.0 ± 0.8 ; $p = 0.02$), and female asthmatics had lower FEV₁ percent predicted values than female nonasthmatics (100.9 ± 3.1 vs. 110.3 ± 0.9 ; $p = 0.002$). No statistically significant difference was found for mean age at the time of most recent testing for asthmatics and nonasthmatics. Asthmatics were, however, taller than nonasthmatics at the last visit (63.4 ± 0.7 cm (standard error of the mean) vs. 61.6 ± 0.3 cm, respectively; $p = 0.04$).

Two analyses were undertaken to evaluate the severity of disease in the asthmatics. Asthmatics diagnosed by the first survey (prevalent cases, $n = 48$) were traced in years 4–13 of the study to determine the frequency of a physician's diagnosis of active asthma. Of these 48 prevalent cases, 13 (27.1 percent) reported an asthmatic diagnosis at least once in the 10-year follow-up. As determined by questionnaire, four of the 91 asthmatics (4.4 percent) were hospitalized at the age of asthma occurrence and nine of the total group (9.9 percent) were ever hospitalized for asthma during the 11 subsequent years of the study. A mean of 1.6 ± 1.0 (standard deviation) hospital admissions for asthma was recorded for those hospitalized. Of the female cases, 17.7 percent ($n = 6$) were hospitalized at least once compared with 5.3 percent of the male cases ($n = 3$) ($p = 0.07$). Fifty-six of the cases (61.5 percent) were medicated for asthma at some time during the follow-up period; the mean number of surveys at which medication use was reported among these children was 3.4 ± 2.5 (standard deviation). Females reported having ever used medication (67.6 percent, $n = 23$) more often than males (57.9 percent, $n = 33$), but the difference was not statistically significant.

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Risk factors

The occurrence or presence, at any time during the study, of respiratory illnesses, atopy, personal or secondary cigarette smoke, delivery complications, parental asthma, and parental atopy is shown in table 1 for asthmatics and nonasthmatics. Asthmatics more frequently reported pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy than nonasthmatics. Prevalent and incident asthmatics had similar occurrences of these factors except hay fever, which was found more often in incident asthmatics than in prevalent asthmatics ($n = 26$ (60.5 percent) vs. $n = 16$ (33.3 percent); $p = 0.01$). At the time of entry into the study, prevalent and incident asthmatics had comparable occurrences of these factors (data not shown).

Sex-adjusted relative risks of asthma associated with these antecedent exposures

are presented in table 2. Significant relative risk estimates were found for pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. All other factors studied bore no apparent relation to the development of asthma (table 2). Although the sex-adjusted relative risk estimate associated with personal smoking did not reach statistical significance, it was of the same magnitude as the other significant estimates. Small numbers may explain the lack of statistical significance. Analyses that used antecedent and antecedent-concurrent covariates produced comparable results. Only antecedent covariates were used in analyses to explore possible causal relations.

Effect modification by illness onset before or after entry into the study was analyzed to evaluate potential recall bias. No statistically significant interaction by time

TABLE 1
Potential risk factors for asthma in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988

Factor	Prevalent asthma ($n = 48$)	Incident asthma ($n = 43$)	Nonasthmatics ($n = 679$)	<i>p</i>
	No. (%)	No. (%)	No. (%)	
Lower respiratory illness				
Pneumonia	18 (37.5)	18 (41.9)	91 (13.4)	≤ 0.001
Bronchitis	20 (41.7)	20 (46.5)	121 (17.8)	≤ 0.001
Bronchiolitis	—*	1 (2.3)	8 (1.2)	0.59
Atopy				
Hay fever	16 (33.3)	26 (60.5)	108 (15.9)	≤ 0.001
Eczema	6 (12.5)	9 (20.9)	73 (10.8)	0.12
Upper respiratory illness				
Sinusitis	14 (29.2)	20 (46.5)	100 (14.7)	≤ 0.001
Croup	5 (10.4)	9 (20.9)	96 (14.1)	0.34
Other factor				
Personal cigarette smoking	10 (20.8)	14 (32.6)	135 (19.9)	0.14
Maternal smoking	34 (70.8)	27 (62.8)	431 (63.5)	0.58
Paternal smoking	26 (54.2)	24 (55.8)	395 (58.2)	0.83
Delivery complications	8 (16.7)	8 (18.6)	92 (13.8)	0.60
Familial factor				
Parental asthma	19 (39.6)	20 (46.5)	178 (26.2)	0.003
Parental atopy	31 (64.6)	31 (72.1)	367 (54.0)	0.03

* No occurrence.

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TABLE 2

Sex-adjusted relative risk of asthma associated with various factors in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988

Factor	Antecedent exposure		Antecedent concurrent exposure	
	Sex-adjusted relative risk	95% confidence interval	Sex-adjusted relative risk	95% confidence interval
Lower respiratory illness				
Pneumonia	3.77	2.29-6.20	4.42	2.83-6.91
Bronchitis	2.66	1.64-4.31	3.22	2.09-4.97
Bronchiolitis	—*	—*	—*	—*
Atopy				
Hay fever	4.44	2.17-9.08	8.17	4.56-14.64
Eczema	1.39	0.67-2.91	1.68	0.89-3.17
Upper respiratory illness				
Sinusitis	3.60	1.74-7.44	4.33	2.30-8.17
Croup	0.88	0.36-2.16	0.99	0.45-2.14
Other factor				
Personal cigarette smoking	2.29	0.67-7.88	2.82	0.98-8.09
Maternal smoking	1.09	0.68-1.74	1.18	0.76-1.83
Paternal smoking	1.20	0.62-2.31	1.14	0.63-2.06
Delivery complications	1.27	0.74-2.19		
Familial factor				
Parental asthma	1.95	1.29-2.95		
Parental atopy	1.61	1.03-2.50		

* No occurrence.

of entry was found (data not shown). Pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy remained the only significant sex-adjusted predictors detected. In addition, the effect of interval assignment for the onset of covariate illnesses and asthma occurring in the "gap" years was analyzed. No significant differences in relative risk estimates for the occurrence of asthma by interval assignments were found (data not shown). Therefore, all further analyses were performed by assigning illness onset in the "gap" years as the age of the child at year 4 of the study.

A proportional hazards model was constructed that included the six sex-adjusted covariates that were found to be significantly associated with asthma (table 3). Bronchitis, hay fever, and parental asthma were the only significant predictors after adjusting for sex and other covariates in

TABLE 3

Relative risk of asthma associated with significant environmental and familial factors, as estimated by multiple regression, in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988

Factor	Relative risk	95% confidence interval
Sex (male/female)	2.39	1.35-4.23
Pneumonia (yes/no)	1.38	0.67-2.88
Bronchitis (yes/no)	3.62	1.94-6.77
Hay fever (yes/no)	2.92	1.20-7.08
Sinusitis (yes/no)	2.21	0.88-5.52
Parental asthma (yes/no)	2.43	1.38-4.29
Parental atopy (yes/no)	1.44	0.84-2.48

the model. Based upon the estimated covariances of the parameter estimates, the correlation between the coefficients was -0.39 for pneumonia and bronchitis, -0.30 for hay fever and sinusitis, and -0.23 for parental asthma and parental atopy.

Figure 1 graphically illustrates the importance of selected predictors to the cumulative incidence of asthma, by age, using parameter estimates from the full data set. Panel A shows the unadjusted Kaplan-Meier estimates (22) of the cumulative incidence function for the cohort. In this plot, 10.6 percent of the population is shown to have developed asthma by age 12. Based on the adjusted model presented in table 3 and assuming no identified risk factors, males had a greater cumulative incidence of asthma than did females by this age (7.2 percent vs. 3.1 percent; panel B). Furthermore, 23.8 percent of males with bronchitis before age 1 but no other risk factors and 10.8 percent of females with a similar respiratory history had asthma by age 12 (panels C and D).

The possibility that sex altered the associations of the individual risk factors and asthma was evaluated (table 4). Females had a greater risk for the occurrence of asthma associated with all individual risk factors except for bronchitis. Statistical significance, however, was detected only for this interaction of sex and parental asthma and atopy.

Two additional analyses were performed to examine the plausibility of a causal relation between asthma and other illnesses. First, four proportional hazards models were constructed that used bronchitis, pneumonia, hay fever, and sinusitis, respectively, as the dependent variable with asthma as one of the independent covariates (table 5). If significant relations were seen in these "reversed" models, it

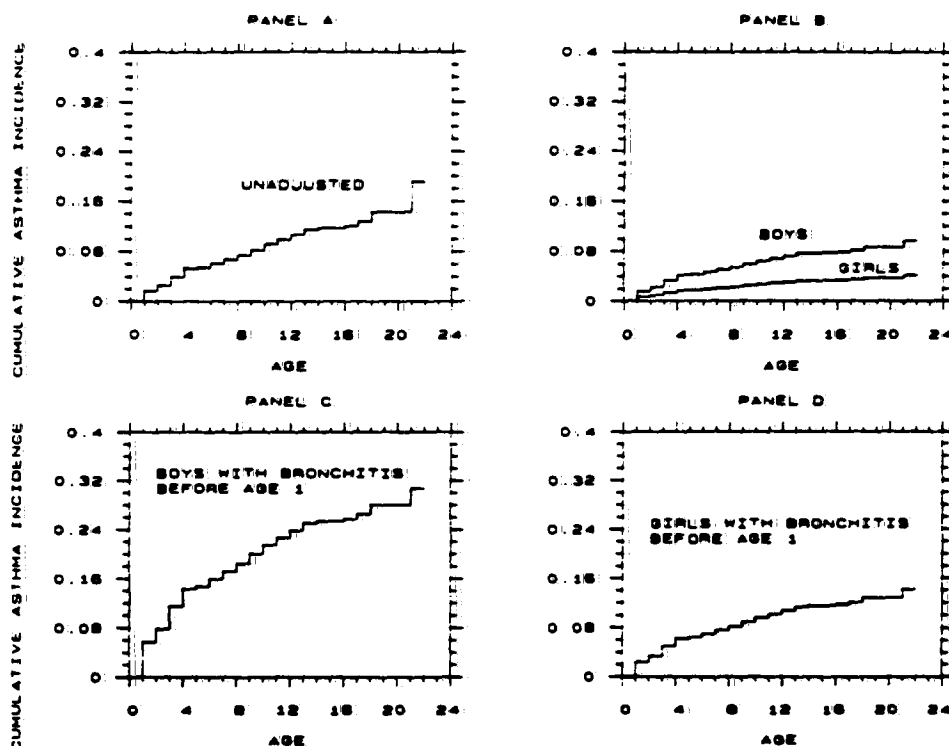


FIGURE 1. Cumulative incidence of asthma, by age, in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988. Panel A, incidence unadjusted for risk factors; Panel B, incidence for children with no risk factors, by sex; Panels C and D, incidence for children who had bronchitis before age 1 year but no other risk factors.

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would suggest that asthma and the illnesses were occurring at about the same time in childhood, rather than sequentially as in a causal model. Asthma was not identified as a significant covariate in models that defined bronchitis or pneumonia as the outcome variable, but it was a statistically significant risk factor for hay fever and sinusitis (table 5).

In the second analysis, simple cross-tabulations were prepared showing the temporal relations between age of onset of asthma and other illnesses for those individuals who developed both. More subjects had the occurrence of bronchitis ($n = 25$ vs. $n = 7$) and pneumonia ($n = 22$ vs. $n =$

7) before, rather than after, the occurrence of asthma, whereas twice as many subjects had the occurrence of hay fever ($n = 11$ vs. $n = 22$) and sinusitis ($n = 10$ vs. $n = 20$) after and not before the occurrence of asthma. Additionally, bronchitis was a significant risk factor for the development of pneumonia, while hay fever and sinusitis were both significant predictors of each other (data not shown). This analysis would suggest that bronchitis and pneumonia as well as hay fever and sinusitis are indistinguishable from one another as predictors.

The risk of asthma associated with any of the individual covariates did not vary by parental asthma or parental atopy (data not shown). However, several interesting trends were seen. The risk of asthma was greatest in subjects with hay fever or sinusitis if they had parental asthma and in subjects with bronchitis or pneumonia if they did not have parental asthma. Additionally, the risk of asthma was greatest in subjects with pneumonia or bronchitis if they had parental atopy.

The effect of age at first occurrence of asthma (age <10 years or ≥ 10 years) on the relations of the individual risk factors and asthma was assessed (data not shown). This age categorization was chosen because parents answered all questions for children younger than 10 years of age. Again, no

TABLE 4
Interaction of sex and significant environmental and familial factors for asthma in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988

Factor	Relative risk		p
	Male	Female	
Environmental factor			
Pneumonia (yes/no)	3.03	3.85	0.63
Bronchitis (yes/no)	4.23	2.46	0.35
Hay fever (yes/no)	2.37	4.80	0.24
Sinusitis (yes/no)	1.73	3.83	0.24
Familial factor			
Parental asthma (yes/no)	0.52	3.13	0.0002
Parental atopy (yes/no)	0.57	3.02	0.014

TABLE 5
Sex-adjusted relative risk of upper and lower respiratory illnesses associated with asthma in a longitudinal study of 770 children aged 5-9 years, East Boston, Massachusetts, 1975-1988

Dependent variable	Independent covariates	Relative risk	95% confidence interval
Bronchitis	Sex (male/female)	1.14	0.84-1.56
	Asthma (yes/no)	2.08	0.95-4.51
Pneumonia	Sex (male/female)	1.11	0.78-1.58
	Asthma (yes/no)	1.93	0.88-4.21
Hay fever	Sex (male/female)	1.03	0.74-1.43
	Asthma (yes/no)	2.64	1.66-4.18
Sinusitis	Sex (male/female)	1.19	0.84-1.70
	Asthma (yes/no)	2.18	1.34-3.54

statistically significant difference was found by age of first occurrence of asthma for the relations of any of the individual covariates and asthma. However, point estimates for hay fever and sinusitis were larger before age 10 (9.46 vs. 3.06 and 4.95 vs. 3.10, respectively), while point estimates for bronchitis and pneumonia were greater at or after age 10 (2.46 vs. 2.97 and 3.69 vs. 3.87, respectively).

DISCUSSION

This investigation focused on the quantitative effects of a number of factors that are thought to be associated with and possibly causally related to the occurrence of asthma. Unlike many previous studies, it paid special attention to the temporal relation of the potential risk factors and the occurrence of asthma. The cohort of study children, 5- to 9-year-olds at intake, came from a stable, relatively homogeneous population. The self-report of a physician's diagnosis of asthma determined disease outcome. The asthmatics so identified in this study were similar to other previously described school-aged asthmatics (5, 6, 11-16). They were diagnosed at a young age and had reduced FEV_1 and FEF_{25-75} percent predicted values compared with the non-asthmatics (5, 13, 23). The severity of disease was mild, as is documented by the findings that only 9.9 percent of the asthmatic group were ever hospitalized and 61.5 percent were ever medicated in the 13 years of the study. Most of the prevalent asthmatics (62.5 percent) did not report a further diagnosis of asthma, which is in close agreement with the 65.9 percent rate reported in the National Child Development Study (11) and the 70 percent rate reported from Australia by McNicol and Williams (13).

Sex differences were evident in the asthmatic group. More males than females reported a diagnosis of asthma. Additionally, males were diagnosed more frequently at younger ages and had less extreme disease,

as measured by fewer hospitalizations recorded. Clear male/female differences were evident for the effect of asthma on lung function level. Male asthmatics had larger FVC percent predicted and female asthmatics had lower FEV_1 percent predicted than their counterparts. Thus, even after adjusting for differences in height and age, there were male/female differences in level of lung function. The meaning of these differences is unclear and requires further investigation.

The results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences. The exact mode of genetic transmission for asthma is still unknown. Autosomal dominance with incomplete penetrance (24) and polygenic inheritance (25) are thought to be the most likely modes of genetic expression. This study was not designed to evaluate specific genetic pathways, but the findings do provide some insight into the interplay between atopy and asthma in first-degree relatives and the development of asthma in childhood. Parental asthma and atopy were both significant bivariate predictors for childhood asthma, which reaffirms the observation that asthma clusters in families (26) and can be inherited as part of a general allergic susceptibility (27, 28). Parental asthma was a stronger predictor than parental atopy, a finding that agrees with previous studies that have shown that parental atopy may enhance the likelihood for the expression of asthma but does not, on its own, impart as great a risk as does parental asthma (25, 29, 30). These data suggest that inheritance of asthma and atopy overlap but are not identical. Females were more likely to develop asthma than males if they had a parental history of asthma or atopy. The significance of this finding is unclear and requires further research.

Four antecedent respiratory illnesses increased the risk of asthma in childhood. Bronchitis, pneumonia, hay fever, and si-

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nusitis all showed significant sex-adjusted relative risk estimates. Bronchitis and hay fever were the most important predictors detected after adjusting for the effects of the other individual covariates. This result, however, must be interpreted with caution, since bronchitis and pneumonia or hay fever and sinusitis are often clinically indistinguishable from each other. Furthermore, bronchitis was predictive of pneumonia and hay fever and sinusitis were each predictive of the other in the Cox models, indicating a high correlation between these variables.

The mechanisms by which bronchitis, hay fever, pneumonia, or sinusitis may cause asthma remain speculative. Bronchitis may act directly by inducing structural changes in the airways (31) or causing alterations in autonomic control of smooth muscle tone (32, 33), leading to increased levels of airway responsiveness and hence to the onset of asthma. In the study population, asthma occurred more often after bronchitis and was not a significant predictor for the occurrence of this illness. Both of these findings would support a possible direct mechanism. A direct pathway for hay fever is less feasible, but indirect mechanisms can be postulated. Hay fever may alter breathing patterns and allow more sensitizing agents (e.g., cold air, aeroallergens) access to the airways, which in turn may increase asthma expression. Alternatively, subjects with a tendency to develop hay fever may also be at risk for developing asthma. Asthma occurred more often before hay fever and was a significant predictor for the occurrence of hay fever. Thus, a direct biologic pathway may be responsible for the development of asthma in nonatopic subjects, while an indirect pathway may be operating in atopic children (34). This hypothesis requires further testing, however, since no direct measures of atopy (i.e., skin testing, immunoglobulin E levels) were obtained in this investigation. Diagnostic misclassification may explain the significance of pneumonia and sinusitis as risk factors for the occurrence of asthma. Of

course, subjects with these illnesses may also be indirectly at risk for developing asthma.

A familial predisposition for asthma did not influence the associations between significant covariate predictors and the onset of asthma. Low study power and crude inheritance markers may explain this finding. It is interesting, nonetheless, to examine the parameter estimates from this analysis. Bronchitis had a much greater effect on the development of asthma in subjects without parental asthma. This again supports the concept that injury to the airways, in and of itself, may be sufficient to cause asthma. Hay fever was a stronger predictor in individuals with parental asthma, implying that the expression of asthma and atopy may be interrelated.

Many infectious and environmental factors were not predictive of asthma. It is noteworthy that bronchiolitis and croup were not found to be significant predictors of asthma in this study. These results contrast with those of previously reported studies (3, 4, 9, 35). This finding may reflect a lower occurrence rate and/or a milder expression of these diseases in the East Boston community compared with the other groups studied. An additional possibility is that croup and bronchiolitis are collinear with pneumonia and bronchitis. Alternatively, these respiratory illnesses occurring early in life may be of relevance only for asthma onset at an early age, and the study may lack sufficient power to detect this. Delivery complications had little effect on the risk of asthma and may indicate the imprecise measurement of this variable.

None of the cigarette smoking variables were predictive of asthma. Parental smoking may have resulted in exposure levels too low to increase the risk of asthma. This seems unlikely given previous findings of the relation of parental smoking to wheezing symptoms in children and reduced levels of lung function in asthmatic children (36). Another possible explanation is that

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parental smoking may be not causal but a modifier of the severity of asthma in children with this disorder. In addition, parents in households with wheezing children may have altered their smoking habits. A self-selection factor may explain the lack of significance for personal smoking. Children with hyperresponsive airways may not be able to tolerate the irritating effects of tobacco smoke. Additionally, the low prevalence of personal smoking in this age group may have resulted in reduced statistical power.

Asthma remains a disease that defies definition partially because of the heterogeneity of clinical expression. A self-report of a doctor's diagnosis of asthma, as obtained from a standardized questionnaire, is widely used to identify persons with asthma for epidemiologic research (37-39). Nonetheless, in children, using this definition may result in underdiagnosis of asthma. Taussig et al. (40) concluded from a study of the diagnostic criteria used by Tucson clinicians that considerable overlap of chronic bronchitis and asthma existed. Furthermore, Speight et al. (41) found that asthma was diagnosed in only a small proportion of English schoolchildren with a history of wheezing and bronchial responsiveness to histamine. To the extent that underreporting has occurred in this study, estimates of relative risk for asthma are conservative and are biased toward the null value. A similar argument can be made for self-reporting of a doctor's diagnosis of the other upper and lower respiratory illnesses studied.

Current concepts of asthma as a disease incorporate measures of bronchial hyperresponsiveness. Nonspecific airways responsiveness to cold air challenge has been assessed in a subset of the asthmatics used in these analyses. In a cross-sectional study, Weiss et al. (42) found that 11 of 12 asthmatics with any wheezing in the study year had increased bronchial responsiveness using a cutoff value for cold air challenge of a greater than 9 percent decrease

in prechallenge FEV_1/FVC . The one asthmatic not responding had a borderline 8 percent decrease in FEV_1/FVC . Increased responsiveness was also significantly associated with a history of previous asthma. Thus, in this population, the definition of asthma appears to be very sensitive.

The study was designed to avoid several potential biases. Selection bias was not evident, as community and not hospital- or physician-referred participants were enrolled in the study. Preferential recall bias could have been present for those asthmatics diagnosed before entry into the study. Asthmatics or their parents may have been more likely to recall previous respiratory or atopic illnesses at the initial survey. It is unlikely, however, that this could explain our findings, since no effect modification by illness onset before or after study entry was detected. Physicians in the study community could have been more likely to diagnose a child as asthmatic given a parental history of asthma or atopy and frequent episodes of bronchitis, pneumonia, hay fever, or sinusitis. This potential bias could not be directly evaluated.

Associations found in this study met most of the standard epidemiologic criteria for causality (43, 44). An appropriate time sequence of cause before effect was assured by the study definition of exposure and by the use of time-dependent covariates in the analyses. The study results demonstrated consistency with replication. Risk factors for asthma identified by these analyses were similar to those found by several other community-based studies (11-16). Strong associations were found, as is seen by the large relative risk parameter estimates for the significant covariates. The strength of these associations would suggest that bias is less likely to explain the findings. Asthma is a multifactor disease, and therefore specificity of association would not be expected to be upheld. Dose-response relations were not evaluated, and biologic coherence, as previously discussed, remains speculative but plausible.

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In conclusion, several risk factors for the development of childhood asthma have been identified. This study improved upon the methodology used in other population-based studies by ensuring antecedent exposures and by minimizing the effects of selection bias and preferential recall bias.

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Weitzman, M., Gortmaker, S., Walker, D.K., Sobol, A. "Maternal Smoking and Childhood Asthma" Pediatrics 85(4): 505-511, 1990.

ABSTRACT. According to a substantial literature, passive smoking by children is associated with an increased incidence of lower respiratory illness and diminished pulmonary function. The relationship between passive smoking and childhood asthma, however, is not clear. Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed with information about 4331 children aged 0 to 5 years to study the relationship between maternal smoking and (1) the prevalence of childhood asthma, (1)[sic] the likelihood of taking asthma medication, (3) the age of onset of children's asthma, and (4) the number of hospitalizations among children with and without asthma. An odds ratio for asthma of 2.1 was shown by multivariate logistic regressions among children whose mothers smoke 0.5 packs of cigarettes or more per day compared with children of nonsmokers ($P=.001$). In similar analyses maternal smoking of 0.5 packs per day was identified as an independent risk for children's use of asthma medications (odds ratio 4.6, $P=.0006$) and for asthma developing in the first year of life (odds ratio 2.6, $P=.0006$). Maternal smoking is also associated with increased numbers of hospitalizations by its association with an increased risk of asthma as well as by contributing to hospitalizations independently of a child having asthma. Among children with asthma, however, maternal smoking is not associated with increased numbers of hospitalizations. It was concluded that maternal smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease. These findings have implications for renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives.

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Maternal Smoking and Childhood Asthma

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ABSTRACT. According to a substantial literature, passive smoking by children is associated with an increased incidence of lower respiratory illness and diminished pulmonary function. The relationship between passive smoking and childhood asthma, however, is not clear. Data from the Child Health Supplement to the 1981 National Health Interview Survey were analyzed with information about 4331 children aged 0 to 5 years to study the relationship between maternal smoking and (1) the prevalence of childhood asthma, (2) the likelihood of taking asthma medication, (3) the age of onset of children's asthma, and (4) the number of hospitalizations among children with and without asthma. An odds ratio for asthma of 2.1 was shown by multivariate logistic regressions among children whose mothers smoke 0.5 packs of cigarettes or more per day compared with children of nonsmokers ($P = .001$). In similar analyses maternal smoking of 0.5 packs per day was identified as an independent risk for children's use of asthma medication (odds ratio 4.6, $P = .0006$) and for asthma developing in the first year of life (odds ratio 2.6, $P = .0006$). Maternal smoking is also associated with increased numbers of hospitalizations by its association with an increased risk of asthma as well as by contributing to hospitalizations independently of a child having asthma. Among children with asthma, however, maternal smoking is not associated with increased numbers of hospitalizations. It was concluded that maternal smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease. These findings have implications for renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives. *Pediatrics* 1990;85:505-511; maternal smoking, asthma, passive smoking.

The contribution of cigarette smoke to indoor air pollution¹ and the adverse health consequences of

passive smoking²⁻⁵ have recently come to be recognized as major public health problems. Estimates vary, but children living in temperate climates spend 60% to 80% of their time indoors⁶ and approximately 70% of all children in the United States live in homes where there is at least one adult smoker.^{5,7} According to a growing literature, increased childhood respiratory symptoms and altered respiratory function are associated with parental smoking. In general, it has been found in these studies that maternal smoking is more strongly correlated with children's respiratory dysfunction than is paternal smoking.⁸⁻¹³ The most frequently offered explanations for this finding are that fathers spend less time at home than do mothers and that children spend more time with their mothers than their fathers. Hence, children are more likely to be exposed to passive smoke if their mothers smoke than if their fathers smoke. In at least two recent articles, however, it was suggested that maternal smoking during pregnancy may have independent effects on children's pulmonary structure and function.^{14,15}

Among preschool children, the finding most frequently documented to date is an increased rate of lower respiratory infection and respiratory symptoms in children less than 2 years of age whose mothers smoke.^{12,13,16-18} In most studies this association was shown to weaken or disappear as children grow older.^{12,16-18} It was demonstrated in a further series of studies that maternal smoking is associated with diminished lung size¹⁹ and decreased pulmonary function as measured by forced expiratory volume in 1 second, forced vital capacity, or forced expiratory flow, mid-expiratory phase among older children, thus suggesting long-term negative effects on children's pulmonary function.^{4,11,20-26}

Although the consensus of the literature is that passive smoking is harmful to children, the rela-

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tionship between parental smoking and the prevalence and severity of childhood asthma remains unclear. There are few studies of childhood asthma and maternal smoking in which large population-based data sets were used, and none that we are aware of in which a nationwide sample was used. Previous studies have been fairly evenly divided between those in which an increased prevalence of childhood asthma or chronic wheeze associated with parental smoking^{8,10,22,27-29} was demonstrated and those in which it was not.^{12,16,30-34}

We analyzed data from the Child Health Supplement to the 1981 National Health Interview Survey to study the relationship between maternal smoking and (1) the prevalence of childhood asthma among children aged 0 to 5 years, (2) the likelihood of taking asthma medications prescribed by a physician, (3) the age of onset of children's asthma, and (4) the numbers of overnight hospitalizations.

METHODS

In the National Health Interview Survey, a complex, multistage probability sampling design was used to provide a representative sample of the civilian noninstitutionalized population of the United States. In the 1981 survey there was a Child Health Supplement in which data were collected concerning one randomly chosen child in each eligible household. The supplement included 15 416 children aged birth to 17 years, of whom 4331 were aged 0 to 5 years, and contained data concerning maternal smoking. All information was derived from parent reports; there were no medical examinations of children or reviews of medical records. The interview contained a series of questions concerning family sociodemographic characteristics and a list of 59 chronic health conditions, including asthma, that children might have. Parents were asked if the index child had ever had asthma, if the asthma lasted for at least 3 months, whether the child still had asthma or if it has been cured, and how old the child was when asthma was first noticed. Children were categorized as having asthma if their parents reported that it was present at the time of the interview, had been present for more than 3 months, and had not been cured. Parents were also asked a series of questions about the age of the child at onset of asthma. In a separate series of questions, parents were asked whether the child had taken an asthma medication prescribed by a physician in the past 2 weeks. Children reported as having taken such medication for asthma were categorized as current users of asthma medications.

Questions were also asked about maternal smoking during pregnancy for all sample children aged

0 to 5 years. In other studies it has been indicated that women who smoke during pregnancy tend to continue to smoke following pregnancy.³⁵ Thus, the measure of maternal smoking used in these analyses includes both prenatal and postnatal exposure. No questions were asked about paternal smoking.

In previous studies^{36,37} it was found that parent reports tend to overestimate the prevalence of clinically diagnosed chronic conditions; however, this overreporting tends to decline with the severity or perceived stigma of the conditions. The majority of population-based studies of childhood asthma have relied on parent reporting for the identification of children with asthma. Some authors³⁸ believe that exclusive dependence on physician reporting results in significant underreporting of childhood asthma. In one study³⁸ 96% of school-aged children with asthma could be identified by parent reporting; in another³⁹ parent reports of children's asthma were confirmed in 94% of patients,³⁹ and in another⁴⁰ it was shown that parent reports of childhood asthma are a good indicator of impaired ventilatory function.

Statistical Analysis

All survey responses were weighted when we calculated means and proportions using the weights provided by the National Center for Health Statistics, which reflect the probability of selection, non-response, and poststratification adjustments. *T* tests were used to evaluate differences in means and χ^2 tests were used to measure differences in proportions. Logistic regressions were also estimated when the dependent variable was dichotomous using the PC SAS CATMOD program. The coefficient estimates can be interpreted as odds ratios associated with the predictor variable. Multivariate linear regressions were used when the dependent variable was the number of overnight hospitalizations.

Estimates of statistical significance were made assuming simple random sampling. The actual sampling design was stratified, multistage, and clustered, and the assumption of simple random sampling in this case will result in overestimates of statistical significance. We expect that design effects will be as great as 1.5. For this reason, we only discuss associations significant at the .01 level or less.

RESULTS

As shown in Table 1, 26% of children's mothers reported smoking during pregnancy. Of these, 13% smoked less than a half-pack of cigarettes per day and 13% smoked a half-pack or more per day. Rates

and intensity of maternal smoking were substantially different for different subsets of women. Less educated women and women who report lower incomes were more likely to smoke and were more likely to smoke a half-pack of cigarettes or more per day than were more educated or more affluent women.

Asthma was reported as being present in 2.3% of children whose mothers did not smoke, 2.6% of children whose mothers smoked less than a half-pack of cigarettes per day, and 4.8% of children

whose mothers smoked a half-pack or more per day ($P = .001$, Table 2). In Table 3, the relative odds ratio for asthma among children aged 0 to 5 years is shown according to maternal smoking behavior. Compared with mothers who did not smoke, the odds ratio for children whose mothers smoked less than a half-pack per day is 1.1 and the comparable ratio for children whose mothers smoked a half-pack of cigarettes or more per day is 2.1 ($P = .001$). When we used a multivariate analysis with a logistic regression model controlling for sex, race, presence

TABLE 1. Maternal Smoking During Pregnancy, 1981 National Health Interview Survey (n = 4538)*

	No. of Mothers	No Smoking	Smoke < 1/2 Pack Day	Smoke ≥ 1/2 Pack Day
Race				
Black	632	74	18	8
White	3555	73	13	14
Other	144	90	9	**
Family income (\$)				
<10,000	1053	64	19	17
10,000-25,000	1868	75	13	12
25,000+	1139	80	9	10
Maternal education				
<High school	1033	62	19	19
High school	1930	71	15	14
Some college	756	84	9	7
College	598	92	5	3
All children	4331	74	13	13

* Sample sizes will vary because of missing data. Results are given as percentages.

† Estimate not reported because number in cell is less than five observations.

TABLE 2. Prevalence of Asthma and Current Use of Asthma Medications Among Children Aged 0 to 5 Years by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)

Maternal Smoking Status	No. of Mothers	Prevalence of Asthma (%)	P Value	% of Children Currently Using Asthma Medications	P Value
No maternal smoking	3210	2.3		0.5	
Maternal smoking < 1/2 pack/d	574	2.9	.68	*	
Maternal smoking ≥ 1/2 pack/d	547	4.8	.001	2.0	.0003
All children	4331	2.7		0.7	

* Estimate not reported because number in cell is less than five observations.

TABLE 3. Relative Odds Ratio for Asthma and Current Use of Asthma Medications Among Children Aged 0 to 5 Years by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)

Maternal Smoking Status	Bivariate Analysis				Multivariate Analysis*			
	Asthma	P Value	Use of Asthma Medication	P Value	Asthma	P Value	Use of Asthma Medication	P Value
No maternal smoking	1.0		1.0		1.0		1.0	
Maternal smoking < 1/2 pack/d	1.1	.68	†		1.2	.55	†	
Maternal smoking ≥ 1/2 pack/d	2.1	.001	4.1	.0003	2.1	.005	4.7	.0006

* Control variables include sex, race, presence of both parents, family size, and number of rooms in household.

† Estimate not reported because number in cell is less than five observations.

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both biologic parents, family size, number of rooms in household, and maternal education, the odds ratios are 1.2 and 2.1, respectively ($P = .006$, Table 3). Family income did not add significantly to this equation at $P < .05$.

We examined the relationship between maternal cigarette smoking and the prevalence of children reported as using a physician-prescribed asthma medication in the past 2 weeks. Overall, 7 per 1000 children 0 to 5 years of age were reported to be using asthma medications. The prevalence of asthma medication use was strongly associated with maternal smoking: the odds of a child using asthma medication was 4.1 times greater if the mother smoked a half-pack or more of cigarettes per day compared with nonsmokers ($P = .0003$, Table 2). When multivariate controls were introduced to control for potential confounding variables, the odds ratio was 4.7 ($P = .0006$). Control variables included sex, race, presence of both biologic parents, family size, number of rooms in the household, and maternal education. Family income did not add explanatory power to this equation.

We also estimated the association between cigarette smoking of the mother and the reported onset of asthma in the first year of the child's life. The prevalence of onset of asthma in the first year of life was 4.5% if the mother smoked a half-pack or more per day, and 1.6% if she did not smoke ($P = .0001$). Multivariate logistic regressions indicated an odds ratio of 2.6 if the mother smoked a half-pack or more of cigarettes per day ($P = .0006$, Table 4).

Because of concern that parents might mistakenly report respiratory illnesses associated with wheezing as asthma among children less than 2 years of age, we investigated the relationship between maternal smoking and asthma and use of asthma medications among children aged 2 to 5 years. With multivariate analyses, again controlling for sex, race, presence of both biologic parents, family size, number of rooms, and maternal education, we saw an odds ratio of 1.9 for asthma ($P = .003$) and 3.6 for the use of asthma medications ($P = .01$) for children whose mothers smoke a half-pack of cigarettes or more per day compared with children whose mothers do not smoke.

We also examined the reported number of overnight hospitalizations among children and their relationship to maternal smoking. There was a strong relationship of hospitalizations to maternal smoking (Figure). For children without asthma this relationship was highly statistically significant ($P = .0001$) and changed little when controls for socioeconomic variables were introduced. For the children with asthma, the relationship between mater-

nal smoking and number of hospitalizations was not statistically significant.

DISCUSSION

These data from the population-based Child Health Supplement to the 1981 National Health Interview Survey indicate that maternal cigarette smoking is associated with higher rates of asthma, an increased likelihood of using asthma medications, and an earlier onset of the disease among children 0 to 5 years of age, independent of a number of other potentially confounding variables. Children whose mothers smoke one half-pack of cigarettes or more per day are twice as likely to have asthma and are four times as likely to use asthma medications as are children whose mothers do not smoke. The data also demonstrate that 26% of American children live in households with mothers who report smoking during pregnancy. Currently 26% of American adults smoke (*Time*, April 18, 1988:71-90); thus, rates of prenatal and early childhood passive exposure to maternal cigarette smoke are comparable with rates of active smoking among adults in the United States.

All information in this study is based on parent reports of asthma and smoking; hence, the results should be interpreted with some caution. Questions

TABLE 4. Relative Odds Ratio for Onset of Asthma in the First Year of Life by Maternal Smoking Status, 1981 National Health Interview Survey (n = 4331)*

Maternal Smoking Status	Onset of Asthma in First Year of Life	P Value
No maternal smoking	1.0	
Maternal smoking < 1/2 pack/d	.85	.39
Maternal smoking \geq 1/2 pack/d	2.6	.0006

* Control variables include sex, race, presence of both parents, family size, number of rooms in household, and maternal education.

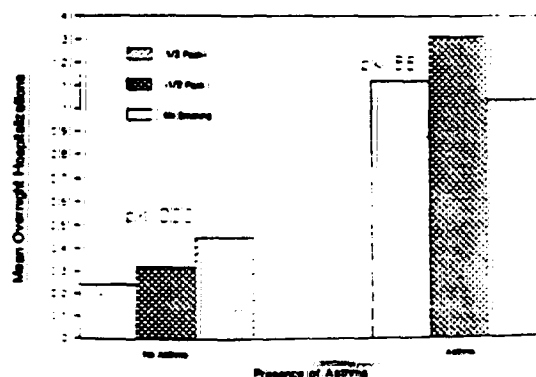


Figure. Hospitalizations by maternal smoking and asthma, children ages 0 to 5 years, 1981.

about maternal smoking were only asked in families with children aged 0 to 5 years; therefore, it is not possible to generalize these results to older children or to investigate whether more prolonged childhood exposure is associated with still higher rates of asthma or increased asthma-associated morbidity. Also, no information is available concerning maternal respiratory symptoms. In previous studies,^{16,41} an increased incidence of respiratory symptoms was shown among adult smokers, and other studies have indicated that parent reports of their children's respiratory symptoms are influenced by their own respiratory symptoms. Physical examinations would not necessarily have resulted in more accurate reporting of children with asthma, because signs and symptoms of asthma are often intermittent and many children with asthma have normal baseline respiratory status between attacks. Similarly, information from medical records is notoriously incomplete.

The lack of a relationship between passive exposure to maternal cigarette smoke and hospitalizations among children with asthma in this study is puzzling. Although in occasional studies⁴² there is failure to demonstrate increased bronchial reactivity among children with asthma exposed to passive smoke, in the majority of laboratory studies to date increased bronchial reactivity seems to be a fairly consistent response to passive smoking by asthmatics. The studies provide a physiologic basis for the belief that passive smoking exacerbates childhood asthma. There is surprisingly little clinical or population-based data, however, to support this belief. According to O'Connell and Long,⁴³ parents reported that their smoking aggravated their children's asthma and that the children's asthma improved when they stopped smoking. Murray and Morrison¹¹ reported 47% more symptoms among children with asthma whose mothers smoked. Tsimoianis et al²⁴ found increased cough reported among 12- to 17-year-old nonsmoking athletes who had parents who smoked cigarettes. None of these studies, however, specify number of bed days or hospitalizations. Fergusson and Horwood¹² and Dodge²⁷ found no association between passive smoking and exacerbations of children's asthma. Evans et al⁴⁴ reported a 63% increase in emergency room use by children with asthma associated with smoking by one or more family member; however, they failed to demonstrate an association between passive smoking and days with asthma symptoms, hospitalization rates, or pulmonary function. The findings from the National Health Interview Survey also do not demonstrate an association between maternal smoking and increased hospitalizations among children with asthma. This finding must be

viewed with particular caution, however, because with only 117 children with asthma in the sample, its statistical power is low. For example, to detect a difference in hospitalization rates of 10% (with 80% power and an α of .05), a sample three times larger than the present one is required.

The mechanism by which maternal smoking is associated with an increased prevalence of childhood asthma is currently not known. In most studies to date children's respiratory symptoms, asthma, and lung growth were correlated with postnatal passive smoking, but in several recent studies it was suggested that antenatal exposure to tobacco smoke might have separate, independent effects on pulmonary development and function. Collins et al¹⁴ provided rat model data that suggest that maternal cigarette smoking during pregnancy is characterized by fetal lung hypoplasia with decreased lung volume and decreased numbers of alveoli. In another study¹⁵ it was demonstrated that maternal smoking during pregnancy is associated with elevated cord blood IgE among newborns of nonallergic parents and a fourfold increased risk of the development of atopic disease (asthma, eczema, urticaria, or food allergy) before 18 months of age, suggesting that maternal smoking during pregnancy predisposes even low-risk infants to subsequent sensitization, probably in synergy with a subsequently acquired mucosal damage that would facilitate penetration of foreign matter. The estimate of children's exposure to cigarette smoke in the current study is crude, based on parent reporting of smoking during pregnancy. It seems reasonable to assume that for most mothers smoking habits remain relatively stable from pregnancy through early childhood and there is at least one study³⁸ to support this contention. Our data are certainly consistent with earlier findings indicating prenatal and postnatal effects on pulmonary structure and function, but it was not possible to differentiate prenatal from postnatal maternal smoking effects on the prevalence of childhood asthma.

IMPLICATIONS

In three landmark reports by the Surgeon General^{2,3} and the National Academy of Sciences⁴ and the recent article by Fielding and Phenox,⁵ similar conclusions were presented about the adverse effects of passive smoking. Although passive smoking appears to present smaller risks than active smoking, the number of people injured by passive smoking is much larger than the number injured by other environmental agents that are already widely regulated. The American Academy of Pediatrics Committee on Environmental Hazards⁶

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has stated that passive smoking may be the most important source of environmental contamination and some believe that it is the most important environmental factor involved in the etiology of early asthma.⁴⁶ It is extremely unlikely that we will ever be willing or able to regulate the smoking of adults in their own homes; therefore, we must employ strategies other than coercion to help parents decrease their smoking, both for their own health as well as for their children's well-being.

The findings of this study should encourage renewed efforts to discourage smoking in families, especially during pregnancy and the first 5 years of children's lives. It is suggested that pediatricians may actually be able to help prevent childhood asthma if they can help parents stop smoking. Strategies that may be useful include explaining the environmental hazards of smoking to children, especially the association between maternal cigarette smoking and the increased risk of a child having asthma; encouraging parents not to smoke; and referring parents who smoke to smoking cessation programs. Low-cost smoking cessation programs for pregnant women have been shown to be effective,⁴⁷⁻⁴⁹ but such programs have not been widely implemented or used. Two barriers to their use are the fact that insurance carriers and Medicaid generally do not pay for these programs, and physicians do not tend to refer patients to them.

The Committee on Environmental Hazards of the American Academy of Pediatrics⁴⁵ suggests that physicians routinely inquire about parental smoking habits when caring for children with chronic or recurrent respiratory symptoms. The data reported in this paper, when viewed in the context of other recent studies, suggest that this advice is not broad enough. Parents should be encouraged not to smoke, irrespective of their child's current respiratory status, or their smoking may result in the development of asthma in their children.

ACKNOWLEDGMENTS

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FANNY FARMER DIDN'T COOK UP THIS HASH

Hashing - basically an excuse to run on a surprise-filled trail and finish with beer, food and song - has reached the U.S. after years overseas, mostly in the Far East. Based on the 18th-century English school-boy game called hares and hounds, hashing was dreamed up in the 1930's by two Englishmen and an Australian living in what is now Malaysia. The trio sought to shed some pounds and shrug off a few hangovers by running around a Kuala Lumpur park.

But mere running was little dull. So the trio decided to take turns laying trails - littered with false leads - through jungles and rice fields. After navigating the course, they rewarded themselves, rather to the detriment of their original purpose, with beer in their quarters next to a club nicknamed the Hash House. (As some hashers tell it, the club barred the sweaty runners because they didn't meet its dress code.) And the hash was born.

In the ensuing decades, hashing spread among international bankers, military personnel, diplomats and others who tended to find themselves in places like Brunei with nothing to do. Now there are 80 000 hashers in more than 700 clubs in 126 countries on every continent except Antarctica.

Stout H. Following the flour is a popular sport for folks on the run. *The Wall Street Journal*. October 11, 1989.

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Rubin, B.K. "Exposure of Children with Cystic Fibrosis to Environmental Tobacco Smoke" The New England Journal of Medicine 323(12):782-788, 1990.

ABSTRACT: Background - In children, passive exposure to environmental tobacco smoke has been associated with growth suppression and an increased frequency of respiratory tract infections. On the assumption that this association would be more pronounced in children with chronic pulmonary disease, we examined the growth, nutritional status, lung function, and clinical condition of children with cystic fibrosis in relation to their exposure to environmental tobacco smoke. Methods - We studied 43 children (age, 6 to 11 years) on entry to a summer camp and then again after two weeks in this smoke-free environment. Twenty-four of the children (56 percent) came from homes with smokers. Results - There appeared to be a dose-dependent relation between the estimate of smoke exposure (cigarettes smoked per day in the home) and overall severity of disease, as assessed by the age-adjusted rate of hospital admissions ($r = 0.58$), peak expiratory flow rate ($r = -0.39$), and measures of growth and nutrition, including weight percentile ($r = -0.37$), height percentile ($r = -0.44$), midarm circumference ($r = -0.42$), and triceps skin-fold thickness ($r = -0.31$). These effects were most evident in the girls. When only the 24 children from homes with smokers were analyzed, however, the dose-dependent relation was present only for the number of hospital admissions and for height. Among the children with good lung function ($n = 21$) or with normal weight for height ($n = 27$) at the start of camp, those who had been exposed to tobacco smoke gained significantly more weight during the two weeks of camp than did the children from smoke-free homes. Conclusions - These data suggest that passive exposure to tobacco smoke adversely affects the growth and health of children with cystic fibrosis, although the possibility cannot be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children.

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EXPOSURE OF CHILDREN WITH CYSTIC FIBROSIS TO ENVIRONMENTAL TOBACCO SMOKE

BRUCE K. RUBIN, M.D., F.R.C.P.(C.)

Abstract Background. In children, passive exposure to environmental tobacco smoke has been associated with growth suppression and an increased frequency of respiratory tract infections. On the assumption that this association would be more pronounced in children with chronic pulmonary disease, we examined the growth, nutritional status, lung function, and clinical condition of children with cystic fibrosis in relation to their exposure to environmental tobacco smoke.

Methods. We studied 43 children (age, 6 to 11 years) on entry to a summer camp and then again after two weeks in this smoke-free environment. Twenty-four of the children (56 percent) came from homes with smokers.

Results. There appeared to be a dose-dependent relation between the estimate of smoke exposure (cigarettes smoked per day in the home) and overall severity of disease, as assessed by the age-adjusted rate of hospital admissions ($r = 0.58$), peak expiratory flow rate ($r = -0.39$), and measures of growth and nutrition, in-

cluding weight percentile ($r = -0.37$), height percentile ($r = -0.44$), midarm circumference ($r = -0.42$), and triceps skin-fold thickness ($r = -0.31$). These effects were most evident in the girls. When only the 24 children from homes with smokers were analyzed, however, the dose-dependent relation was present only for the number of hospital admissions and for height. Among the children with good lung function ($n = 21$) or with normal weight for height ($n = 27$) at the start of camp, those who had been exposed to tobacco smoke gained significantly more weight during the two weeks of camp than did the children from smoke-free homes.

Conclusions. These data suggest that passive exposure to tobacco smoke adversely affects the growth and health of children with cystic fibrosis, although the possibility cannot be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children. (*N Engl J Med* 1990; 323:782-8.)

EXPOSURE to environmental tobacco smoke has been postulated to have an adverse effect on lung function¹⁻⁴ and growth⁵⁻¹¹ in normal children. There is a dose-dependent relation in the frequency of respiratory tract infections in infants and young children exposed to tobacco smoke.¹⁻³ Some studies have shown a statistically significant decline in pulmonary function in healthy children exposed to tobacco smoke,¹² and

there is a suggestion that children with asthma have more frequent attacks and more severe disease when exposed to environmental tobacco smoke.³ There is also a body of evidence relating growth retardation and weight reduction to active smoking in adults^{13,14} as well as to passive smoking in children⁷⁻¹¹; a similar relation has been found in infants born to mothers who smoke⁵⁻⁷ and in infants born to mothers passively exposed to tobacco smoke.¹⁵

Cystic fibrosis is an autosomal recessive disease whose major manifestations are recurrent and chronic pulmonary infections and pancreatic malabsorption

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with growth retardation.^{16,17} Children with this disease may therefore be at increased risk for harm from exposure to tobacco smoke. We studied the relation between exposure to smoke and clinical status, growth and nutrition, and pulmonary function in a group of children between the ages of 6 and 11 years attending a summer camp for children with cystic fibrosis. The camp setting was ideal for collecting information about the children's medical history and exposure to tobacco smoke. Furthermore, this setting facilitated the organized collection of data on growth, nutrition, and pulmonary function on entry into camp and the assessment of changes in these measurements after two weeks of a balanced, high-quality diet, carefully administered medications, and physiotherapy in an environment free of tobacco smoke.

METHODS

At the start of the two-week summer camp for patients with cystic fibrosis (Camp Merrywood in eastern Ontario), a medical history was obtained for each camper as part of the registration process, and all had a physical examination, which included the measurement of height, weight, and routine vital signs. After informed consent was obtained from the parents or guardians of the campers, a group of physicians, nurses, and medical students from Queen's University (Kingston, Ont.) and the University of Ottawa cystic fibrosis centers collected additional data on 43 of the 46 campers as detailed below. Incomplete data were collected for one boy who left early (for family reasons) and another who arrived a day late. One of the campers declined participation in the study. This study was approved by the March of Dimes, which coordinates Camp Merrywood, by the administrators of the camp, and by the Queen's University Human Research Committee.

The medical history was supplemented by a questionnaire that was completed by the parents. Data were collected about the severity of the camper's illness (e.g., frequency of cough, amount of sputum, and number of hospital admissions) and about his or her home, including a listing of all household members, their ages, health status (including recent respiratory tract infections), and tobacco consumption, expressed as the number of cigarettes smoked per day in the home. These data were checked for accuracy by reviewing the questionnaire both with the parent who completed the form and with the child. Historical data were further verified by cooperating Ontario cystic fibrosis centers after camp was completed.

In each participating child, midarm circumference and triceps skin-fold thickness were measured (skin-fold spring-loaded caliper, John Bull British Indicators),¹⁸ and pulmonary function was evaluated (Vanguard spirometer and recorder, Life Support and Equipment). Clinical progress was assessed with the Shwachman-Kulczycki system,¹⁶ which uses historical data and physical-examination results to calculate a score for the general, nutritional, and physical health of patients with cystic fibrosis. All the children were familiar with pulmonary-function testing procedures. Spirometry was repeated until three acceptable curves were produced for each child,¹⁹ from which forced vital capacity (FVC), forced expiratory volume in one second, peak expiratory flow rate (PEFR), and expiratory flow rate measured between 25 percent and 75 percent of the forced vital capacity were recorded from the curve in which the total of FVC and forced expiratory volume in one second was largest. Pulmonary-function data were analyzed after camp by computer and expressed both in terms of absolute volumes and flow rates and as the percentages of the predicted values for Ontario children of the same height and sex.¹⁹ The physical examination, spirometry, and anthropomorphic measurements were repeated on the last day of camp. The investigators who conducted the physical examinations, evaluated pulmonary function, and collected nutritional data were unaware of the details of the medical history — specifically, the children's exposure to tobacco smoke.

Statistical analysis was performed with the StatView 512+ statistics package (Abacus Concepts) and a Macintosh II computer (Apple Computer) and reviewed by a statistician. Comparisons between children who were exposed to environmental tobacco smoke and those who were not were made with an unpaired *t*-test. Changes in pulmonary function and nutritional status in the two groups of children while they were at camp were analyzed with an unweighted, two-tailed, paired *t*-test. Analysis of variance was used to investigate the interaction between exposure to environmental tobacco smoke and growth. Results are presented as means \pm SD. All *P* values of less than 0.05 were considered to indicate significance.

One severely ill child required constant nasal administration of oxygen and was unable to participate in camp activities. Because this girl spent most of the camp session in the infirmary, initial data related to her growth and health were recorded, but she was excluded from analyses dealing with changes noted after camp.

RESULTS

Patient Population and Severity of Illness

The children were 72 to 143 months of age (mean, 108.9 ± 16.7) and had been seen at one or more of the seven cystic fibrosis centers in Ontario. There were 18 girls and 25 boys in the group that completed the study. Twenty-four of the children (56 percent) came from households with smokers (24.4 ± 14 cigarettes smoked in the home per day), and nearly 40 percent had mothers who smoked (18.6 ± 9.2 cigarettes per day). None of the children actively smoked.

Clinical scores indicated that as a group these children were in fairly good health. Of a possible total of 25 points, the Shwachman-Kulczycki general score for the group was 23.2 ± 3.1 , the physical score was 22.0 ± 4.3 , and the nutrition score was 22.1 ± 4.0 . There was a correlation between the total score and the number of cigarettes smoked in the home ($r = -0.34$, $P = 0.03$), but this was accounted for almost entirely by the strong correlation between the nutrition subscore and exposure to environmental tobacco smoke ($r = -0.41$, $P = 0.006$).

Because the total number of hospitalizations increases with the age of the patient, one measure of illness severity is the normalized hospital-admission rate, obtained by dividing the total number of admissions by the child's age in months. Normalization of the admission rate minimizes the effect of the broad age range of the children and more accurately reflects the severity of illness. In the group as a whole, the normalized hospital-admission rate was strongly related to the number of cigarettes smoked in the home ($r = 0.58$, $P < 0.0001$) (Fig. 1). Examining data from just the 24 children exposed to tobacco smoke still yielded a significant, dose-dependent relation ($r = 0.55$, $P < 0.01$). There was a significant correlation of exposure to tobacco smoke with the normalized hospital-admission rate for the girls ($P = 0.0005$), and analysis of variance suggested that this factor alone accounted for 57 percent of the variability. Somewhat surprisingly, the relation between exposure to tobacco smoke and the normalized hospital-admission rate was not significant for the boys.

We further compared subgroups of children according to lung function: 21 had relatively normal lung

function, as defined by an FVC of more than 80 percent of the predicted value, and 20 had impaired function (FVC <80 percent of the predicted value). (Vital capacity could not be measured in two children.) Children with poorer lung function had significantly more hospitalizations if there was smoking in the home (8.4 vs. 1.7 admissions; $P = 0.05$). We also compared the children with good nutritional status, as indicated by a weight for height more than 50 percent of the predicted value ($n = 27$), with those with poor nutritional status (weight for height <50 percent of the predicted value; $n = 16$), and there was a trend for more hospitalizations in malnourished children from homes with smokers (6.4 vs. 1.8 admissions for malnourished children from homes without smokers; $P = 0.1$).

Effect of Tobacco Smoke on Pulmonary Symptoms and Function

There was no association between exposure to tobacco smoke, expressed as the number of cigarettes smoked in the home per day, and the amount of coughing or sputum production, the number of nasal polyps, or any pulmonary-function measurement except the percentage of predicted PEFR ($r = -0.39$, $P = 0.01$). The association with PEFR was stronger in the girls ($r = -0.53$, $P = 0.03$) and was also more clearly evident in children with good lung function (95.7 percent for those exposed to tobacco smoke as compared with 118.4 percent for those not exposed; $P = 0.01$). There was also a weak association between the degree of digital clubbing, as measured on a four-point scale (none, mild, moderate, or severe),

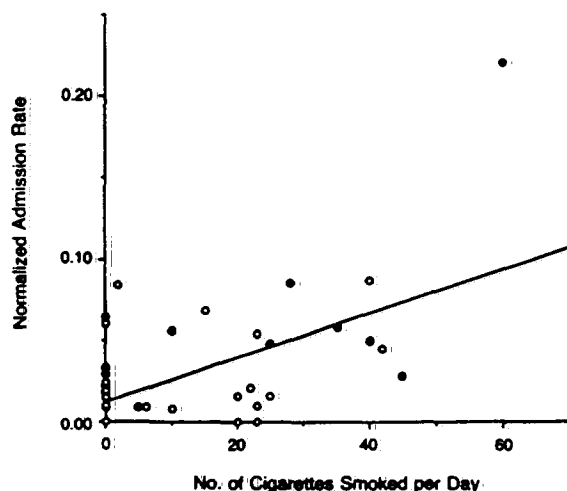


Figure 1. Normalized Admission Rate (Number of Hospital Admissions Divided by the Age of the Child in Months) as a Function of the Number of Cigarettes Smoked in the Home.

The values for the group of 43 children as a whole were $r = 0.58$ and $P < 0.0001$; for the 18 girls, $r = 0.76$ and $P = 0.0005$; for the 25 boys, $r = 0.15$ and $P = 0.50$; and for the 24 children from homes with smokers, $r = 0.55$ and $P < 0.01$. Girls are represented by solid circles, and boys by open circles.

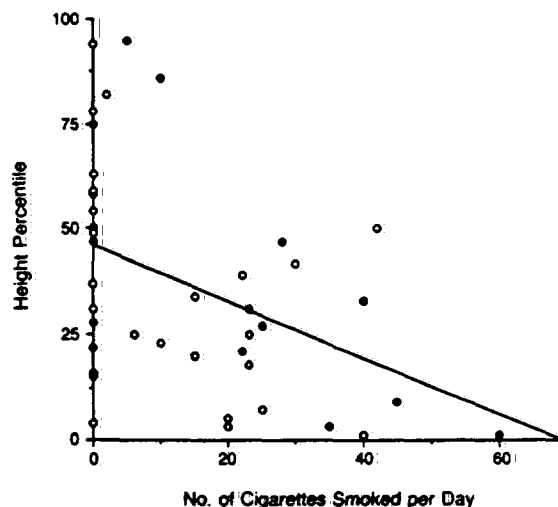


Figure 2. Children's Height Percentiles as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were $r = -0.44$ and $P = 0.003$; for the girls, $r = -0.58$ and $P = 0.01$; for the boys, $r = -0.37$ and $P = 0.07$; and for the group of children from homes with smokers, $r = 0.52$ and $P < 0.01$. Girls are represented by solid circles, and boys by open circles.

and the number of cigarettes smoked in the home ($r = 0.30$, $P = 0.05$).

Effect of Environmental Tobacco Smoke on Growth and Nutrition

Exposure to tobacco smoke was associated most strongly with growth and nutrition (Fig. 2 through 5); a dose-dependent relation was observed for all measurements when the analysis included children not exposed to tobacco smoke (exposure level of 0). The group not exposed to tobacco smoke averaged about the 50th percentile for age for both height and weight.

For the girls there was a significant relation ($P < 0.05$) between the amount of exposure to tobacco smoke and the height percentile (25 percent of the variability) and weight percentile (33.9 percent of the variability), whereas for the boys there was a trend toward significance correlating exposure to tobacco smoke with the height percentile ($P = 0.067$; 13.8 percent of the variability) but no significant relation with the calculated weight percentile at the start of camp.

There was a significant correlation between exposure to tobacco smoke and both the child's height ($r = -0.61$, $P < 0.0001$) and the height percentile according to age and sex (Fig. 2). This relation was still valid when only the 24 children from homes with smokers were considered ($r = 0.52$, $P < 0.01$). The dose-dependent relation between exposure to tobacco smoke and height was stronger for the girls ($r = -0.82$, $P < 0.0001$) than for the boys ($r = -0.42$, $P = 0.03$). A similar correlation was noted between the child's weight and the number of cigarettes smoked in the home for the entire group of children ($r = -0.55$, $P = 0.0002$) and for the girls only

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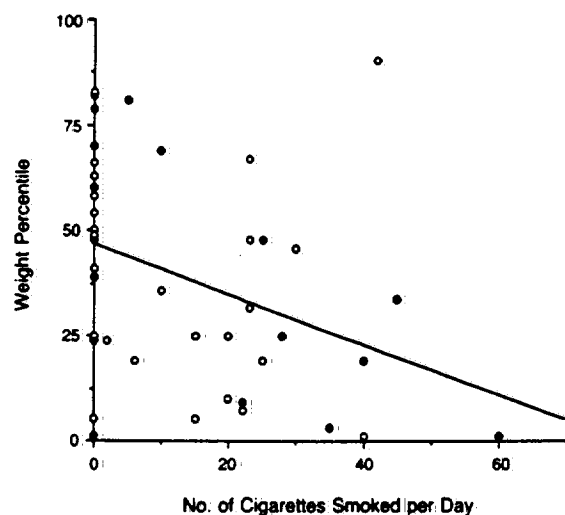


Figure 3. Children's Weight Percentiles as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were $r = -0.37$ and $P = 0.01$; for the girls, $r = -0.50$ and $P = 0.03$; for the boys, $r = -0.12$ and $P = 0.57$; and for the group of children from homes with smokers, $P = 0.36$. Girls are represented by solid circles, and boys by open circles.

($r = -0.77$, $P = 0.0002$), whereas there was a trend toward significance for the boys ($r = -0.33$, $P = 0.11$). There was a dose-dependent inverse correlation between the number of cigarettes smoked by family members each day and the weight percentile according to age and sex (Fig. 3), the midarm circumference (Fig. 4), and triceps skin-fold thickness (Fig. 5), but these correlations failed to achieve significance when data only for the children from homes with smokers were analyzed.

Changes after Two Weeks at Camp

During the two-week camp session significant changes were observed in measures of growth and nutritional status. These included gains in weight, weight percentile, weight-for-height percentile, triceps skin-fold thickness, and midarm circumference. Eight children lost weight over the two weeks of camp, and 29 gained weight. Those who gained weight came from homes where more cigarettes were smoked (mean number of cigarettes smoked daily, 16, as compared with 1.9 cigarettes for those who lost weight; $P < 0.02$).

While at camp children from homes with smokers gained more weight than children from smoke-free homes, especially if their initial FVC was normal (Table 1) or weight-for-height percentile was more than the 50th percentile (Table 2).

DISCUSSION

For more than 30 years, nicotine has been known to be a potent regulator of weight in both humans and animals. Tobacco smokers weigh less than non-smokers^{13,14} and gain an average of 5 kg after they stop

smoking,²⁰ half in the first seven weeks.²¹ Children exposed to tobacco smoke are smaller and lighter than their peers.^{2,21} A strong inverse relation between children's height and the number of smokers at home was found for a sample of children in Great Britain, even when growth was adjusted for birth weight, social class, and parental height. This stunting was also unrelated to respiratory symptoms.⁸ In a study of children in California, it was shown that exposure to environmental tobacco smoke had a significant ($P < 0.001$) inverse and dose-dependent effect on the length at birth and the height at the age of five years that was unrelated to socioeconomic factors.⁹ In Canadian children with normal birth weights, those exposed to environmental tobacco smoke were significantly shorter and lighter between the ages of 1 and 6.5 years than those who were not exposed.¹¹

Children with cystic fibrosis tend to have low birth weights, and their mean height and weight during childhood are lower than those for the general population.^{17,22-24} Although their nutritional requirements are increased, food intake is frequently in the range of 80 percent of the recommended daily allowance of calories and protein for age and height.²² At all ages, female patients with cystic fibrosis have been reported to have a greater degree of growth suppression and malnutrition than male patients.²⁴ The mean height percentile was 38 percent for the group of girls we studied and 36 percent for the boys, but the weight-for-height percentile at the start of camp was 47 percent for the girls and 52 percent for the boys, suggesting that although these children were generally smaller than average, they were not particularly thin.

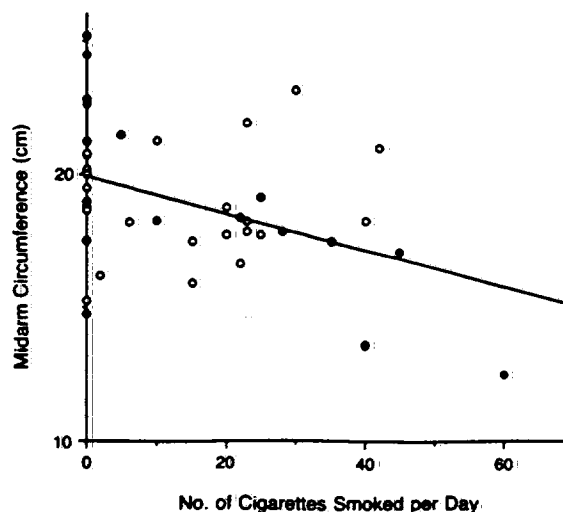


Figure 4. Midarm Circumference as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were $r = -0.42$ and $P = 0.006$; for the girls, $r = -0.68$ and $P = 0.002$; for the boys, $r = -0.17$ and $P = 0.42$; and for the group of children from homes with smokers, $P = 0.10$. Girls are represented by solid circles, and boys by open circles.

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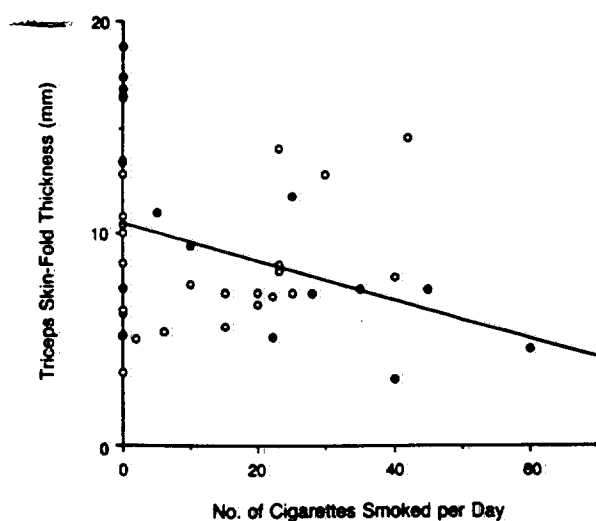


Figure 5. Triceps Skin-Fold Thickness as a Function of the Number of Cigarettes Smoked in the Home.

The values for the entire group were $r = -0.31$ and $P = 0.05$; for the girls, $r = -0.65$ and $P = 0.005$; for the boys, $r = -0.04$ and $P = 0.84$; and for the group of children from homes with smokers, $P = 0.96$. Girls are represented by solid circles, and boys by open circles.

We found that there was a strong dose-dependent relation between exposure to environmental tobacco smoke and all measures of growth and nutrition and that these effects were seen most clearly in the girls. Even the children with normal weight-for-height percentiles were often significantly shorter than average, and this was related to the amount of exposure to environmental tobacco smoke in a dose-dependent manner.

In patients with cystic fibrosis who have malabsorption, bicarbonate secretion from the pancreas is less than 10 percent of the normal value, but patients without gastrointestinal symptoms also have a low level of bicarbonate secretion.²⁵ Studies of conscious dogs given intravenous nicotine equivalent to that in four cigarettes showed a dose-related inhibition of pancreatic and bicarbonate secretions.²⁶ Although nicotine may act by exacerbating malabsorption, we found no difference between the group with smokers in the home and those without in the degree of malabsorption, as measured by stool consistency or the number of enzyme capsules taken daily.

It has been postulated that the weight-regulating effect of nicotine is due to a lowering of the body weight's set-point.²⁷ The satiety center in the ventromedial hypothalamus is thought to be under positive serotonergic control. Pharmacologic treatments that increase serotonin levels or act as agonists at the serotonin receptors decrease food intake.²⁸ Subacute administration of nicotine increases serotonin in the hypothalamus of rats,²⁹ and ventilation of cigarette smoke into isolated, perfused rat lungs decreases the

rate of serotonin inactivation, which in turn increases the level of circulating serotonin.³⁰

Most serotonin is stored in the platelets. Patients with cystic fibrosis tend to have higher mean platelet counts than normal children of the same age regardless of pulmonary status or antibiotic administration.³¹ In a study performed 13 years ago at Camp Merrywood, Partington and Ferguson found that the average blood serotonin level in 67 children with cystic fibrosis was twice that in age-matched controls; however, no correlation was found between serotonin levels and height, weight, or skin-fold thickness.³²

It is possible that there is a relation between lower socioeconomic status, parental smoking, and poor nutrition. Although socioeconomic status was not assessed directly in this study, children exposed to tobacco smoke did not come from larger families than those who were not exposed, nor were there more single-family homes with smokers. Furthermore, in Canada access to health care is not limited by the patient's ability to pay, and health insurance covers nutritional supplements prescribed by a physician. Other studies that have documented an effect of exposure to environmental tobacco smoke on the growth of children have failed to demonstrate a relation with socioeconomic status.^{8,9}

It is also possible that exposure to environmental tobacco smoke further increases the energy expenditure of children with cystic fibrosis beyond their capacity to maintain adequate intake for growth³³; however, the children at camp were generally much more active than they were at home, and yet there was a net gain in weight, midarm circumference, and triceps skin-fold thickness over the two-week session. In all measures of nutrition, the healthiest children from homes with smokers had significantly greater gains than either the children from homes without smokers or the children in poorer health on entry, indicating that some of the effect of tobacco smoke is probably reversible, especially if appropriate weight and lung function can be maintained.

Female patients with cystic fibrosis have poorer nutrition,²⁴ pulmonary function,³⁴ and survival^{24,35} than male patients at every age. There has been much speculation about the reasons for these differences. Although a much greater effect of exposure to tobacco smoke in girls might partially explain this difference, it is just as likely that both environmental tobacco smoke and some other sex-related factors could operate together to suppress the growth and influence the overall health of the female patients.

There are some limitations to the interpretation of these data. Since the children studied chose to attend camp, there could be unknown factors that made this group of children unrepresentative of the general population with cystic fibrosis, even though the summer camp is available free of charge to all children with cystic fibrosis in Ontario between the ages of 6 and 12 years.

Table 1. Characteristics of Children with Cystic Fibrosis, According to Vital Capacity and Exposure to Environmental Tobacco Smoke.

FORCED VITAL CAPACITY*	NO. OF CHILDREN	VALUES AT START OF CAMP				INCREASE DURING CAMP	
		WEIGHT	WEIGHT:HEIGHT	SKIN-FOLD THICKNESS	MIDARM CIRCUMFERENCE	WEIGHT	WEIGHT:HEIGHT
		kg (percentile)	percentile	mm	cm	kg (percentile)	percentile
≥80% of predicted value							
Exposed to smoke	14	25.7 (35.9)	50.9	8.4	18.7	0.85 (6.6)	9.1
Not exposed	7	32.4 (57.3)	74.3	12.8	21.1	0.013 (0.1)	0
P value		0.01 (0.06)	0.05	0.002	0.01	0.12 (0.05)	0.04
<80% of predicted value							
Exposed to smoke	9	25.3 (26.0)	41.8	7.5	17.6	0.63 (2.7)	5.2
Not exposed	11	30.0 (45.8)	49.5	10.5	19.5	0.40 (2.8)	2.9
P value		0.13 (0.12)	0.56	0.18	0.21	0.47 (0.94)	0.40

*Vital capacity could not be measured in two children.

We made no effort to collect blood or urine samples for measurement of biologic markers of exposure to environmental tobacco smoke; however, there is reported to be a strong dose-dependent relation between salivary or urinary cotinine levels and self-reported exposure to tobacco smoke.³⁶ These levels correlated with the number of smokers in the home and the number of cigarettes smoked at home.³⁶ More importantly, we did not obtain information about past smoking by the parents or the duration of parental smoking, so it is possible that several of the children listed as coming from smoke-free homes may have had substantial exposure to environmental tobacco smoke. Studies have suggested that the number of cigarettes smoked daily in the home is more strongly related to the child's height than the number of cigarettes smoked during pregnancy or the length of the child at birth.¹⁰

The absence of an association of pulmonary function with exposure to environmental tobacco smoke in this study could be due to the smallness of the sample; however, the relation between such exposure and pulmonary function in healthy children is open to question^{3,4} and is by no means as clear as the relation between exposure to tobacco smoke and growth.

There was also a strong, dose-dependent relation between exposure to tobacco smoke and the normalized hospitalization rate. We did not record the reasons for the hospitalizations, so it is possible that some were not related to cystic fibrosis. What is more inter-

esting is that although nasal polypectomy is one of the most frequent reasons for surgery in children and adults with cystic fibrosis, there is reported to be an association between nasal polyps and good pulmonary function.³⁷ Although we collected data on the presence or absence of polyps at the time of the initial physical examination at camp, we did not inquire about past polypectomy surgery, nor did we find an association between the presence of nasal polyps and any measurement of nutrition or pulmonary function.

In a recent study of 173 adults with cystic fibrosis, 11 percent regularly smoked tobacco (2 to 60 pack-years), and 20 percent occasionally used marijuana.³⁸ Although a retrospective comparison with non-smokers did not show faster short-term pulmonary deterioration in the tobacco smokers, there was no report of the smokers' nutritional status. The very fact that more than half the children we studied were exposed to tobacco smoke at home and that so many adults with cystic fibrosis could choose to smoke suggests that further studies are needed. It is possible that tobacco smoke decreases appetite and growth in children with cystic fibrosis to a greater degree than in the normal population. If these findings are verified by large, population-based studies, then elucidation of the mechanism of this interaction may have far-reaching implications for our understanding of growth in children with cystic fibrosis, sex differences in the clinical course, and the growth-suppressant effects of tobacco smoke in healthy persons.

Table 2. Characteristics of Children with Cystic Fibrosis, According to Weight-for-Height Percentile and Exposure to Environmental Tobacco Smoke.

WEIGHT FOR HEIGHT	NO. OF CHILDREN	VALUES AT START OF CAMP				INCREASE DURING CAMP	
		WEIGHT	HEIGHT	SKIN-FOLD THICKNESS	MIDARM CIRCUMFERENCE	WEIGHT	WEIGHT:HEIGHT
		kg (percentile)	cm (percentile)	mm	cm	kg (percentile)	percentile
≥50th Percentile							
Exposed to smoke	13	26.3 (37)	125.5 (20.1)	9.3	19.2	0.70 (4.5)	5.4
Not exposed	14	32.6 (58.9)	134.6 (47.7)	13.0	21.1	0.16 (0.1)	0.6
P value		0.004 (0.01)	0.005 (0.003)	0.008	0.03	0.12 (0.03)	0.08
<50th Percentile							
Exposed to smoke	11	24.4 (23.8)	128.7 (42.4)	6.4	17.0	0.80 (5.6)	9.6
Not exposed	5	25.9 (24.2)	132.0 (33.2)	5.6	16.7	0.77 (5.3)	5.8
P value		0.64 (0.98)	0.61 (0.57)	0.49	0.87	0.95 (0.91)	0.47

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Gilljam, H., Stenlund, C., Hollsing, A.E., Strandvik, B. "Passive smoking in cystic fibrosis" Respiratory Medicine 84(4): 289-291, 1990.

SUMMARY: The families of 32 children with cystic fibrosis (CF) were interviewed about both their tobacco consumption and their childrens physical activities. Hospital records informed about treatment frequency, lung function and clinical score. Cystic fibrosis families smoked far more than the Swedish average and the passive smokers among our patients seemed to fare less well in all parameters. The children of smoking mothers required significantly longer periods of intravenous antibiotic treatment ($P > 0.05$). Frequent physical exercise seemed to compensate for the potential harmful effects of passive smoking and children with high physical activity living in families who smoked needed significantly less frequent antibiotic treatment than the inactive children ($P > 0.02$). Although this series is small, the results indicate that a smoke-free environment may be important for CF patients. General information is insufficient and extensive psychological support for the families is probably necessary.

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Passive smoking in cystic fibrosis

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The families of 32 children with cystic fibrosis (CF) were interviewed about both their tobacco consumption and their children's physical activities. Hospital records informed about treatment frequency, lung function and clinical score. Cystic fibrosis families smoked far more than the Swedish average and the passive smokers among our patients seemed to fare less well in all parameters. The children of smoking mothers required significantly longer periods of intravenous antibiotic treatment ($P > 0.05$). Frequent physical exercise seemed to compensate for the potential harmful effects of passive smoking and children with high physical activity living in families who smoked needed significantly less frequent antibiotic treatment than the inactive children ($P > 0.02$). Although this series is small, the results indicate that a smoke-free environment may be important for CF patients. General information is insufficient and extensive psychological support to the families is probably necessary.

Introduction

The hazards of indoor environmental factors are widely recognized. In recent years, investigators have found not only an increased rate of respiratory symptoms and infections in normal children exposed to tobacco smoke (1,2) but also an effect on the children's lung function (3,4). By measuring saliva cotinine levels, parental smoking has been calculated to equal active smoking of at least 80 cigarettes a year (5). Cystic fibrosis (CF) is a chronic hereditary disease that from early infancy drastically increases the risk of serious respiratory infections. A rapid colonization by bacteria, commonly *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* is observed and the airway secretion is abnormally thick and tenacious. Thus, it seems that CF children would be more at risk than others of being affected by passive smoking. Consequently, the following questions were asked: 'Do CF children daily exposed to tobacco smoke in their homes have more frequent airway infections?' 'Do they perform less well in lung function tests or do they have a poorer general state of health than CF children not exposed to tobacco smoke?'

Patients and Methods

This study was approved by the Ethics Committee at Karolinska Institutet.

Thirty-two of 64 CF patients regularly attending the departments of Pediatrics and Lung Medicine at Huddinge Hospital were excluded from the study

since, for example, they no longer lived with their families or lived too far away to be interviewed. The families of 32 CF children aged 1-20 years (mean 10.5, median 12 years) were visited and interviewed by C.S. The interviews were based on a standard questionnaire. Hospital records provided data about antibiotic treatment, lung function tests and the general state of health expressed by the Shwachman score (6). A clinical score of ≥ 71 points was considered good to excellent and a score of less than 71 points mild to serious. We regarded a consumption of 1 cigarette/day or more at home as a smoking family. The patterns of colonization was similar in both groups, as was age and the use of oral antibiotics (penicillinase-stable penicillins and ampicillins). The number of days of antibiotic treatment in hospital during one year was used to measure respiratory infection. This variable was dichotomized into one group with high risk, i.e. ≥ 31 days in hospital with intravenous antibiotics, and one group with low risk, < 31 days in hospital. The lung function was assessed by FEV₁ and a rating of $\geq 70\%$ of predicted value was regarded as good while a rating of $< 70\%$ was considered poor. Physical activity was defined as regular activity on scheduled days each week. Those who were considered highly active had four or more activities during the week and the less active 0-3.

Statistical analysis was made with Chi-square with Yate's correction of Fisher's exact test.

Results

SMOKING HABITS

Twenty-two of the 32 families smoked; in five families both parents smoked; in five families it was

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Table 1 Relation between the clinical score of the CF patients and smoking in the families

Clinical score	Nonsmokers	Smokers	Total
≥ 71	9 (90%)	16 (73%)	25 (78%)
< 71	1 (10%)	6 (27%)	7 (22%)
Total	10 (31%)	22 (69%)	32 (100%)

Table 2 Intravenous antibiotic treatment in CF patients exposed and not exposed to tobacco smoke in their homes

Days of i.v. treatment	Nonsmokers	Smokers	Total
≥ 31	1 (10%)	7 (32%)	8 (25%)
< 31	9 (90%)	15 (68%)	24 (75%)
Total	10 (31%)	22 (69%)	32 (100%)

only the father who smoked; and in eight families only the mother. In three families the mother and one sibling smoked and in one family only siblings. In families where smoking was confined to one room or otherwise restricted in consideration of the child, much fewer cigarettes were smoked than in families where no limits were set. The smoking habits had not changed over time.

PASSIVE SMOKING AND CLINICAL SCORE

Smoking at home appeared to be associated with a poorer health status of the CF child. As shown in Table 1, six out of seven children with a clinical score < 71 lived in smoking families. However, this difference was not statistically significant.

SMOKING AND AIRWAY INFECTIONS

Parental smoking seemed to correlate with an increased tendency for airway infections in CF children (Table 2). The most reliable records of airway infection were judged to be the number of days of i.v. antibiotic treatment in hospital. Seven out of eight patients requiring ≥ 31 days of treatment lived in smoking families and only one in a nonsmoking family. Also in the group of patients demanding less treatment, the exposed children dominated by 15 to 9. In the few families where only one parent smoked, maternal smoking appeared to be more harmful to the patient (Table 3). There was a statistically significant difference between days of treatment if the mother smoked compared to if only the father smoked ($P < 0.05$).

Table 3 Intravenous antibiotic treatment in CF patients exposed and not exposed to tobacco smoke in families with only one parent smoking

Days of i.v. treatment	Mothers		Fathers	
	Nonsmokers	Smokers	Nonsmokers	Smokers
≥ 31	1 (10%)	3 (38%)*	1 (10%)	1 (20%)
< 31	9 (90%)	5 (62%)	9 (90%)	4 (80%)
Total	10	8	10	5

* $P < 0.05$ compared to families where only the father smoked.

Table 4 Intravenous antibiotic treatment in CF patients with low and high physical activity in nonsmoking and smoking families

Days of i.v. treatment	Low activity		High activity	
	Nonsmokers	Smokers	Nonsmokers	Smokers
≥ 31	0 (0%)	5 (45%)*	1 (25%)	2 (18%)
< 31	6 (100%)	6 (55%)	3 (75%)	9 (82%)
Total	6	11	4	11

* $P < 0.02$ compared to patients with high activity living in smoking families.

Table 5 Distribution of FEV₁ values (% of predicted) in CF patients exposed and not exposed to tobacco smoke. Seven of the youngest children could not be assessed and were therefore excluded

FEV ₁ (%)	Nonsmokers	Smokers	Total
≥ 70	5 (71%)	10 (56%)	15 (60%)
< 70	2 (29%)	8 (44%)	10 (40%)
Total	7 (28%)	18 (72%)	25 (100%)

THE BENEFIT OF PHYSICAL ACTIVITY

For patients with high physical activity, passive smoking seemed to matter less (Table 4). The active children had fewer days of hospital treatment than the less active, who required significantly more treatment in hospital if the parents smoked ($P < 0.02$).

PASSIVE SMOKING AND LUNG FUNCTION

The lung function of 25 patients was not correlated to passive smoking (Table 5). Seven of the smallest children had to be excluded as they could not perform a reliable spirometry.

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Discussion

Persons interviewed about their tobacco habits often tend to underestimate their consumption. This is particularly true in situations burdened with guilt like the one investigated here. However, we did not want to increase the burden and therefore only one family member was interviewed and questions about smoking duration and earlier habits also had to be omitted. On the other hand, a high degree of uniformity was achieved by using only one interviewer (C.S.). Despite the small number of patients, the observed trends were evident. Similar effects have been seen in asthmatic children (7). The more pronounced effect of maternal smoking has also been observed earlier (8). It was surprising that so many CF parents smoked; the prevalence of smokers in CF families exceeded the Swedish average by approximately 30% (69% and less than 40%, respectively) (9). The direct acute effects manifested as cough in a smoking environment hardly escapes notice. In addition the doctor had advised against smoking on several occasions. Therefore, profound psychological factors seem to govern the smoking habits. In some smokers the fear of developing lung cancer creates so much anxiety that they smoke even more (9). It is possible that CF parents, by a similar mechanism, may increase their tobacco consumption.

The suggested beneficial effect of physical activity in this study is probably due to activity itself (10), and not to a mere absence from home. It can be argued that the most severely ill patients simply were incapable of being active, but no patient in this series was disabled to that degree and there was no statistical difference in clinical status or pulmonary function between children from smoking and nonsmoking families. This study therefore suggests that passive smoking increases the need for intensive antibiotic treatment in patients with CF

and therefore is detrimental to their health, especially in combination with low physical activity.

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Young, S., Le Souef, P.N., Geelhoed, G.C., Stick, S.M., Turner, K.J., Landau, L.I. "The Influence of a Family History of Asthma and Parental Smoking on Airway Responsiveness in Early Infancy" The New England Journal of Medicine 324: 1168-1173, 1991.

ABSTRACT. Background. Airway responsiveness to inhaled nonspecific bronchoconstrictive agents has been demonstrated in normal, healthy infants. However, it is unknown whether airway responsiveness is present from birth or if it develops as a result of subsequent insults to the respiratory tract. To investigate this question, we assessed airway responsiveness in 63 normal infants at a mean age of 4 1/2 weeks.

Methods. Respiratory function was measured with use of the partial forced expiratory flow-volume technique to determine the maximal flow at functional residual capacity (VmaxFRC). The infants inhaled nebulized histamine at sequentially doubled concentrations (0.125 to 8.0 g per liter), until a concentration was reached at which the VmaxFRC fell by 40 percent from the baseline value (PC40) or until a concentration of 8.0 g per liter was reached. We also assessed maternal serum levels of IgE, cord-serum levels of IgE, the infants' skin reactivity to several allergens, and the parents' responsiveness to histamine and obtained family histories of asthma and smoking.

Results. Airway responsiveness was increased in infants with a family history of asthma (n= 19; median PC40, 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; P<0.01), parental smoking (n= 13; median PC40, 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; P<0.05), or both (n= 20; median PC40, 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; P<0.05), as compared with the infants with no family history of asthma or smoking. The infants with no family history of asthma or smoking had a median PC40 of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00). No significant relations were detected between the immunologic variables and the PC40 in the infants.

Conclusions. This study indicates that airway responsiveness can be present early in life and suggests that a family history of asthma or parental smoking contributes to elevated levels of airway responsiveness at an early age.

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THE INFLUENCE OF A FAMILY HISTORY OF ASTHMA AND PARENTAL SMOKING ON AIRWAY RESPONSIVENESS IN EARLY INFANCY

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Abstract Background. Airway responsiveness to inhaled nonspecific bronchoconstrictive agents has been demonstrated in normal, healthy infants. However, it is unknown whether airway responsiveness is present from birth or if it develops as a result of subsequent insults to the respiratory tract. To investigate this question, we assessed airway responsiveness in 63 normal infants at a mean age of 4½ weeks.

Methods. Respiratory function was measured with use of the partial forced expiratory flow-volume technique to determine the maximal flow at functional residual capacity (V_{maxFRC}). The infants inhaled nebulized histamine at sequentially doubled concentrations (0.125 to 8.0 g per liter), until a concentration was reached at which the V_{maxFRC} fell by 40 percent from the base-line value (PC_{40}) or until a concentration of 8.0 g per liter was reached. We also assessed maternal serum levels of IgE, cord-serum levels of IgE, the infants' skin reactivity to several allergens, and the parents' responsiveness to histamine

and obtained family histories of asthma and smoking.

Results. Airway responsiveness was increased in infants with a family history of asthma ($n = 19$; median PC_{40} , 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; $P < 0.01$), parental smoking ($n = 13$; median PC_{40} , 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; $P < 0.05$), or both ($n = 20$; median PC_{40} , 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; $P < 0.05$), as compared with the infants with no family history of asthma or smoking. The infants with no family history of asthma or smoking had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00). No significant relations were detected between the immunologic variables and the PC_{40} in the infants.

Conclusions. This study indicates that airway responsiveness can be present early in life and suggests that a family history of asthma or parental smoking contributes to elevated levels of airway responsiveness at an early age. (N Engl J Med 1991; 324:1168-73.)

ALTHOUGH asthma is considered to result from a complex interaction of genetic and environmental influences, there has been little recent progress in determining their relative contributions.¹ Recent developments in the measurement of respiratory function in infants² have allowed inhalation challenges to be used in this age group in order to obtain objective measurements of airway responsiveness (the ability of the airways to constrict in response to certain stimuli).³ This technique is of particular interest, since airway responsiveness is the most useful objective physiologic measurement associated with the presence of asthma.¹

The first inhalation-challenge studies in older normal infants, in which investigators used methacholine,⁴ cold, dry air,⁵ or histamine,⁶ indicated that airway responsiveness was present in infants during the first year of life. Two questions have arisen from these studies. First, how early in infancy is airway responsiveness present? It has been speculated that persons with asthma are not born with heightened airway responsiveness but are born with a tendency to increased responsiveness after an insult to the respiratory system.^{1,7} Second, is the initial level of airway responsiveness the same for all infants, or do genetic or environmental influences, or both, result in differing levels of responsiveness at birth? Specific environmen-

tal features, such as viral infections, irritants, and allergens, affect airway responsiveness in older children and adults,¹ but their influence on airway responsiveness in infants is unknown.

To investigate these two questions, we undertook a prospective, longitudinal study to determine the presence and level of airway responsiveness and its relation to a family history of asthma or parental smoking in 63 normal infants. This report presents our findings at the first assessment of the infants, at a mean age of 4½ weeks.

METHODS

Subjects

Sixty-three infants, 24 girls and 39 boys, were studied at a mean age of 4½ weeks (range, 2 to 10). The criteria for inclusion were full-term gestation and an absence of perinatal problems and major congenital anomalies. At the time of the assessment, none of the infants had previously had a lower respiratory tract infection or any clinically important nonrespiratory illness. No infant had had an upper respiratory tract infection in the preceding three weeks. All infants were well at the time of the study.

The families of all the infants were recruited randomly at the prenatal clinic at Osborne Park Hospital, Perth, Western Australia. This is a peripheral metropolitan hospital with 2000 deliveries per year. The recruitment procedure began with an interview with the mother during a routine prenatal visit, at which time she was given written information on the family involvement that would be required during the proposed 12-month study period. One week after the interview, each family was contacted by telephone to determine whether they would agree to participate in the study. Signed parental consent was obtained for all infants. Over a 12-month period, 241 mothers were interviewed and 63 (26 percent) consented to participate. The study was performed with the approval of the medical ethics committees of Princess Margaret Hospital and the University of Western Australia.

Details of respiratory illness and atopy in the family and parental smoking habits were obtained with use of a modified American

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Thoracic Society questionnaire⁸ administered by a single investigator. The 63 infants were divided into four groups on the basis of their family histories of asthma and parental smoking. Those classified as having a family history of asthma were those whose parents reported asthma in primary relatives (the parents and siblings of the infant) or secondary relatives (grandparents, aunts, and uncles). Infants with a family history of smoking were those whose parents reported that either or both had smoked during the pregnancy. The four groups were defined as follows: group 1 ($n = 11$) — no family history of asthma in primary or secondary relatives, both parents nonsmokers; group 2 ($n = 19$) — family history of asthma in primary or secondary relatives (or both), both parents nonsmokers; group 3 ($n = 13$) — no family history of asthma in primary or secondary relatives, one or both parents smoked during the pregnancy; and group 4 ($n = 20$) — family history of asthma in primary or secondary relatives (or both), one or both parents smoked during the pregnancy. The responses to questions about parental smoking habits after the infant's birth indicated that all parents in groups 1 and 2 remained nonsmokers and the smoking parents in one family in group 3 and one in group 4 ceased smoking after the birth of the infant.

Assessment

Responsiveness to histamine was measured in 75 of the parents by the rapid-inhalation technique of Yan et al.⁹ To assess immunologic influences on airway responsiveness, IgE was measured in maternal and cord serum¹⁰ by the Clinical Immunology Research Unit, Princess Margaret Hospital for Children. Forty-seven pairs of samples of maternal and cord serum were analyzed.

Respiratory function was assessed by the forced expiratory flow-volume method.² A jacket was rapidly inflated at end inspiration, and flow was measured from the partial expiratory flow-volume curve at functional residual capacity. The jacket pressure was gradually increased over a series of forced expirations until maximal flow at functional residual capacity (V_{maxFRC}) was obtained. Flow was measured with a No. 1 Fleisch pneumotachograph (PK Morgan, Chatham, England), a Validyne DP-45 pressure transducer (Northridge, Calif.), and a Validyne CD19 amplifier. Volume values were obtained by electronic integration. The infant breathed through a molded-putty face mask attached to the pneumotachograph. All signals were recorded on a chart recorder (Linearecorder F Wr 3801, Graphtec, Tokyo); flow and volume were monitored during the study with a Tektronix 5223 digitalizing storage oscilloscope (Beaverton, Oreg.) and recorded on tape (TEAC SR-50, TEAC Corp., Tokyo). Taped signals were transcribed to paper on a Hewlett-Packard 7090A x,y paper plotter (Waltham, Mass.). Arterial oxygen saturation was monitored throughout the study with a Nellcor N-200 E pulse oximeter (Hayward, Calif.). Supplementary oxygen was administered if arterial oxygen saturation fell below 90 percent.

Infants were studied while asleep after they were given a dose of chloral hydrate (80 mg per kilogram of body weight). The minimal jacket pressure required to produce V_{maxFRC} was established. This pressure was used in all subsequent forced expirations. Respiratory function was assessed before and after the administration of nebulized saline with an Airlife nebulizer (American Pharmaseal, Valencia, Calif.) at 6 liters per minute. This and all other nebulized agents were delivered directly to the face mask and inhaled during one minute of tidal breathing. For the base-line V_{maxFRC} , we used the mean of the values for five forced expirations after the administration of nebulized saline.

The histamine challenge was carried out by administering sequentially doubling concentrations of nebulized histamine, ranging from 0.125 g per liter to a maximal concentration of 8.0 g per liter, as previously described.⁶ A new concentration was delivered every five minutes, and respiratory function was assessed after each, with a minimum of five forced expirations at each measurement. The challenge was ended when a response to histamine was recorded or when the maximal concentration was reached. A response was defined as a decrease in the mean V_{maxFRC} of at least 40 percent from

the base-line value. For infants who responded to histamine, the concentration that provoked a 40 percent decrease in V_{maxFRC} (PC_{40}) was derived by linear interpolation from the plot of the log histamine concentration against the percent decrease in V_{maxFRC} from base line. The coefficient of repeatability for a histamine challenge to an infant according to this protocol was 3.3 sequentially doubled concentrations.¹¹ We also determined the dose of histamine that provoked a 20 percent decline in the forced expiratory volume in one second in the parents (PD_{20}).

Two investigators measured airway function and determined airway response; one, who operated the equipment, was blinded to the infant's family history; the second, who recorded data on the infant's chart, had recruited the participants and completed the family-history questionnaires and was therefore aware of the family history. Because the blinded investigator identified changes in pulmonary function, no bias was introduced into the results.

Skin reactivity was assessed in all infants on the same day as, but before, the administration of chloral hydrate and the subsequent histamine challenge. The allergens used were *Dermatophagoides farinaceus*, perennial ryegrass pollen, cow's milk, and egg white (Hollister-Stier, Elkhart, Ind.). A positive response was defined as a wheal 2 mm or more in diameter.

Statistical Analysis

Differences in base-line values for V_{maxFRC} and PC_{40} among the groups were analyzed with use of the Mann-Whitney U test.¹² The median and confidence intervals for the median were determined with use of the Confidence Interval Analysis microcomputer program.^{13,14} All values for IgE underwent logarithmic transformation before analysis. Within each family-history group, regressions were used to determine the relation between maternal serum IgE levels and cord-serum IgE levels, maternal serum IgE levels and PC_{40} , and cord-serum IgE levels and PC_{40} . Maternal serum and cord-serum IgE levels in the groups were compared with use of Student's unpaired (two-tailed) t-test.

RESULTS

Descriptive data for the groups of infants are shown in Table 1. The infants in group 3 had a significantly lower mean birth weight than those in groups 2 and 4. All the mothers of infants in group 3 smoked during the pregnancy. Among the infants in group 4, 16 had mothers who had smoked during the pregnancy and 4 had fathers who had smoked during this time. There were no significant differences between the birth weights of infants in group 4 whose mothers had

Table 1. Characteristics of the Subjects According to Family-History Group.*

GROUP	BIRTH WEIGHT	WEIGHT†	LENGTH†	AGE†	SEX (F/M)
	kg	kg	cm	wk	
Group 1 ($n = 11$)	3.4 ± 0.5	4.8 ± 0.5	54.1 ± 2.7	3.8 ± 1.9	6:5
Group 2 ($n = 19$)	3.6 ± 0.5‡	5.1 ± 0.7	55.1 ± 2.8	4.8 ± 2.2	6:13
Group 3 ($n = 13$)	3.1 ± 0.4	4.7 ± 0.9	53.8 ± 3.2	4.5 ± 2.2	5:8
Group 4 ($n = 20$)	3.5 ± 0.5‡	4.8 ± 0.7	54.3 ± 2.7	4.6 ± 1.9	7:13

*Plus-minus values are means ± SD. Infants in group 1 had no family history of smoking or asthma; those in group 2 had a family history of asthma but neither parent smoked; those in group 3 had no family history of asthma and at least one parent who smoked; and those in group 4 had a family history of asthma and at least one parent who smoked.

†At the time of the study.

‡ $P < 0.005$ for the comparison with group 3.

§ $P < 0.05$ for the comparison with group 3.

smoked and those of infants whose fathers (but not their mothers) had smoked or those of the infants in groups 1 and 2.

Base-line lung function for the groups is shown in Figure 1. Base-line \dot{V}_{maxFRC} is expressed as a percentage of the predicted value, which was based on the predictive equation of Tepper et al.¹⁵ The four groups did not differ significantly in base-line lung function.

Figure 2 shows the responsiveness to histamine in the four groups. Individual values for PC_{40} are given, along with the median value of PC_{40} for each group. Infants who responded to the first concentration were classified as having a PC_{40} of less than 0.125 g per liter. Those who had not responded at a concentration of 8.0 g per liter were classified as having a PC_{40} of more than 8.0 g per liter. PC_{40} values were not obtained for three infants; two were flow-limited at base line (i.e., forced expiratory flow was no greater than tidal expiratory flow) and therefore were not challenged with

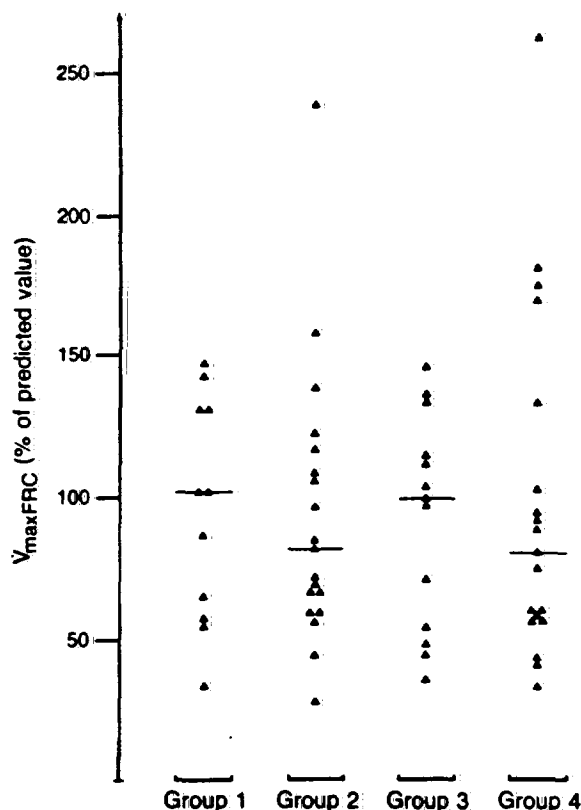


Figure 1: Individual Base-Line Values for \dot{V}_{maxFRC} , Expressed as a Percentage of the Predicted Value for Each Group.

The groups were defined as follows: group 1—no family history of asthma, both parents nonsmokers; group 2—family history of asthma, both parents nonsmokers; group 3—no family history of asthma, one or both parents smoked; group 4—family history of asthma, one or both parents smoked. The horizontal lines show the median percentage of predicted \dot{V}_{maxFRC} for each group. Predicted values, derived with the predictive equation of Tepper et al.,¹⁵ are based on the infants' heights; since one infant's height was not measured, only 19 data points are shown.

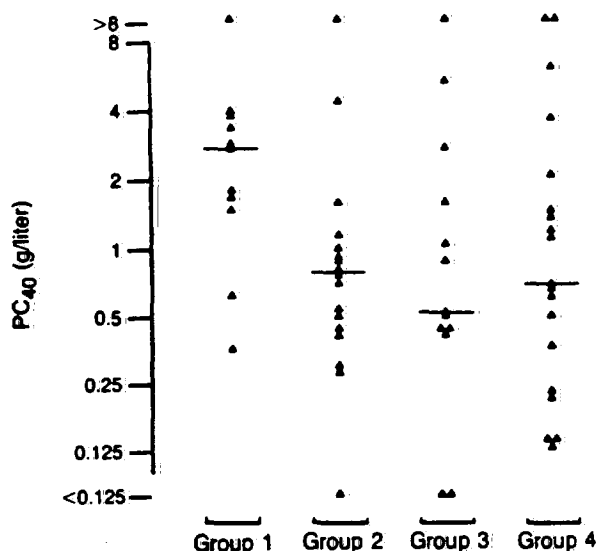


Figure 2: Individual Values for the Histamine Concentrations That Provoked a Decrease of 40 Percent in \dot{V}_{maxFRC} (PC_{40}).

The groups were defined as in Figure 1. The horizontal lines show the median PC_{40} for each group. Two infants in group 2 had base-line flow limitation and therefore could not be challenged with histamine. No PC_{40} value could be determined for one infant in group 4, in whom excessive upper-airway noise developed, necessitating discontinuation of the challenge.

histamine (both in group 2), and in the case of one infant in group 4, the challenge was discontinued when upper-airway obstruction developed. Infants in group 1, who had a median PC_{40} of 2.75 g per liter (95 percent confidence interval, 1.48 to 4.00), were significantly less responsive than those in group 2 (median PC_{40} , 0.78 g per liter; 95 percent confidence interval, 0.44 to 1.15; $P < 0.01$), group 3 (median PC_{40} , 0.52 g per liter; 95 percent confidence interval, 0.43 to 5.40; $P < 0.05$), and group 4 (median PC_{40} , 0.69 g per liter; 95 percent confidence interval, 0.37 to 2.10; $P < 0.05$). There were no significant differences among the values for PC_{40} in groups 2, 3, and 4.

Of the 33 infants who had one or more parents who smoked during the pregnancy (groups 3 and 4), only 4 had fathers who smoked and nonsmoking mothers. All four were in group 4, where a family history of asthma was also present. We were therefore unable to determine the effect of paternal smoking alone.

Because there were more boys than girls in the group as a whole and because there was a particular disproportion in groups 2 and 4, comparisons of airway function were made on the basis of sex. No significant differences were found in either base-line lung function or airway responsiveness between boys and girls in the entire group of 63 infants or within the four family-history groups.

Of the 63 infants in whom skin reactivity was assessed, 7 had a positive response to one allergen and 1 had a positive response to two allergens. Responses were recorded for each of the four allergens and

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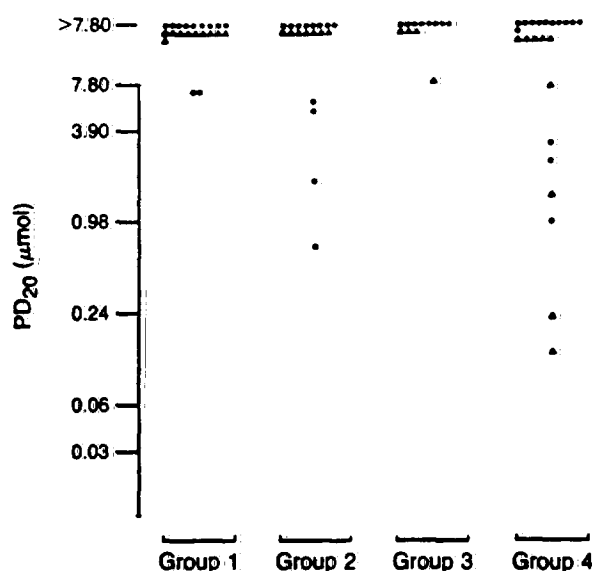


Figure 3. Doses of Histamine That Provoked a Decrease of 20 Percent in the Forced Expiratory Volume in One Second in 75 Parents of Infants in the Four Groups (PD_{20}).

The groups were defined as in Figure 1. Circles indicate mothers, and triangles fathers.

among infants in all four groups. There was no relation between the incidence of skin reactivity and the degree of responsiveness at this age.

Fourteen of the 75 parents who were tested responded to inhaled histamine. The distribution and level of response (PD_{20}) for parents of infants in each of the four groups are shown in Figure 3. There was no relation between the level of parental responsiveness to histamine and the infant's PC_{40} .

For the group as a whole, a significant positive correlation was found between the maternal serum IgE level and the cord-serum IgE level ($P < 0.01$). When each family-history group was analyzed separately, however, this relation was not observed. No significant correlations were found between the maternal serum IgE level and the infant's value for PC_{40} or between the cord-serum IgE level and PC_{40} , either for the entire group of 63 infants or for the four family-history groups. There were no significant differences among the groups in either maternal venous serum IgE levels or cord-serum IgE levels (Fig. 4).

DISCUSSION

The results of this study demonstrate that airway responsiveness to inhaled histamine is present in many normal, healthy infants soon after birth. We also found that the level of airway responsiveness in early life was increased if there was a family history of asthma, parental smoking, or both.

The development of techniques for assessing airway function in infants has made possible the study of airway responsiveness in the first two years of life, a period during which children had not been studied

previously. Prendiville et al.³ showed that infants with recurrent wheeziness were responsive to inhaled histamine. This study was followed by the work of Tepper with methacholine,⁴ Geller et al. with cold, dry air,⁵ and Le Souëf et al. with histamine,⁶ which demonstrated that the airways of normal, healthy, asymptomatic infants were responsive to the same bronchoconstrictive agents routinely used in testing older children and adults. In these studies,⁴⁻⁶ infants were studied well into the first year of life, at mean ages of 8.1 months, 5.6 months, and 7.8 months, respectively. We wished to investigate whether airway responsiveness could be detected in very early infancy. Therefore, in this study we assessed infants at a mean age of 4½ weeks, with some only 2 weeks old. A response to histamine was observed in all but 5 of the 63 infants. This finding indicates clearly that airway responsiveness is present very early in life, and it is not unreasonable to suggest that it may be present from birth.

Another reason for studying infants so early in life is that with increasing age the effect of a number of environmental insults to the airway is likely to increase. These irritants include exposure to cigarette smoke, exposure to allergens, and respiratory tract infections. These respiratory insults are known to increase airway responsiveness in older children and adults,⁷ and it is possible that they also affect airway responsiveness in infants. Therefore, when airway responsiveness is assessed in middle-to-late infancy, exposure to these environmental factors makes it difficult to extrapolate the initial level of airway responsiveness. Studying infants soon after birth should help to minimize, but will not eliminate, this problem.

We found that the level of responsiveness to histamine in infants was related to the presence or absence of a family history of asthma. This finding suggests that the initial level of airway responsiveness may be genetically determined. A genetic effect on airway responsiveness in later life has been established in studies of twins¹⁶ and of the families of persons with asthma.

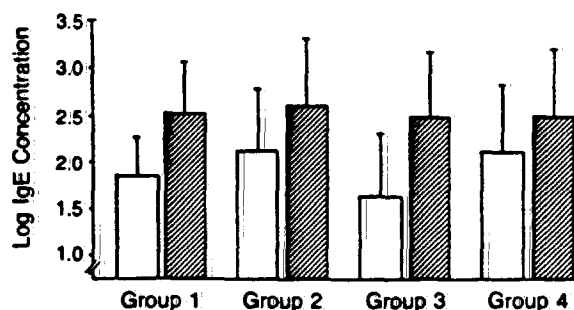


Figure 4. IgE Levels in Cord and Maternal Venous Serum, According to Family-History Group.

The groups were defined as in Figure 1. Open bars indicate mean cord-serum levels, and hatched bars mean maternal venous-serum levels. The T bars indicate the standard deviation.

ma.¹⁷⁻¹⁹ Studies have shown a higher concordance for asthma and atopy in monozygotic twins than in dizygotic twins.¹⁶ Furthermore, other studies have shown a significant relation between a history of asthma in parents and siblings and the development of asthma in early childhood.^{18,19} Our study indicates that a history of asthma in primary or secondary relatives, or both, influences the level of airway responsiveness at an early age.

We also found that airway responsiveness was increased in infants whose parents reported smoking during the pregnancy. Population-based studies of airway responsiveness have found an increase in airway sensitivity among children with asthma whose mothers smoked. Martinez et al.²⁰ recently reported that exposure to tobacco smoke enhanced airway responsiveness in nine-year-old children; bronchial hyperresponsiveness was present in 70 percent of the children whose mothers smoked regularly during the pregnancy, but in only 29 percent of the children whose parents did not smoke during the pregnancy. Since these investigators did not find an overall association between airway responsiveness and current smoking by the mother, they suggested that fetal exposure to tobacco smoke may have had an important effect on airway responsiveness. Our study also demonstrates an association between parental smoking and the level of airway responsiveness in early infancy, although we are unable to separate the effects of prenatal and postnatal exposure to cigarette smoke. The effect of continued postnatal exposure on the base-line level of responsiveness and on the subsequent development of the symptoms of asthma is unknown. Moreover, we have not reported the amount of smoking, since it is widely recognized that the relation between the level of smoking reported by parents and the actual level of passive smoking by the fetus or infant is poor because of underreporting by parents, variations in ventilation in rooms and houses, and differences in the distance between the smoker and the infant.

Base-line lung function, expressed as a percentage of the predicted $\dot{V}_{\max FRC}$,¹⁵ did not differ significantly among the four family-history groups, and no correlation was observed between base-line lung function and PC_{40} . These findings are in agreement with those of studies in humans²¹⁻²³ and animals^{24,25} that have suggested that the caliber of the airway at base line may not be an important factor in responsiveness.

Many studies have been conducted to determine the usefulness of serum IgE levels measured at birth and during infancy in predicting the development of atopic diseases, including asthma, and skin reactivity.²⁶⁻³¹ These studies have indicated that a high IgE level is, in general, associated with atopy; however, all investigators have noted a wide range of IgE levels, with considerable overlap, between subjects with and without atopy. In our study, the infant's IgE level

did not predict the initial level of airway responsiveness or skin reactivity, either for the group as a whole or for the four family-history groups individually. This lack of relation between atopic markers and airway responsiveness may be due to the fact that the infants were assessed before sufficient exposure to allergens had occurred. Bryant and Burns,³² in a study of the relation between atopic status and airway responsiveness to histamine, found no correlations between serum IgE levels and the number of positive skin-prick responses or the level of airway responsiveness in a group of adults with asthma and normal adults.

Correlations have previously been found both between IgE levels in parents and those in infants²⁶ and between a family history of atopic diseases and the infant's IgE level.^{26-31,33} We found a significant positive correlation between maternal and cord-serum IgE levels for the group as a whole, but these two measures did not discriminate among infants with different family histories. These data suggest that allergic markers are not strongly related to the initial level of airway responsiveness at this age. Because these infants are part of a longitudinal study, the potential role and relative importance of these immunologic markers may be clarified as they grow older.

In summary, we found that airway responsiveness to inhaled histamine was often present in normal, healthy, asymptomatic infants early in life. We suggest that responsiveness is present from birth and is determined both by inheritance and by exposure to parental cigarette smoking. The relation of this initial level of airway responsiveness to future levels of responsiveness, respiratory problems, and immunologic markers after exposure to environmental insults during infancy remains to be clarified.

We are indebted to the staff of the prenatal clinic and the State Health Pathology Laboratory at Osborne Park Hospital for their assistance; to Karen Krska of the Clinical Immunology Research Unit, Princess Margaret Hospital for Children, for performing the IgE assays; and to Amanda Reese, B.Sc., and Debra Turner, B.Sc.(Hons.), Department of Respiratory Medicine, for technical assistance.

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PARENTAL SMOKING AND OTITIS MEDIA IN CHILDREN

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OTITIS MEDIA ("GLUE EAR")

In addition to claims that parental smoking affects the respiratory health of children, there are claims that exposure to parental smoking might increase the risk of otitis media (commonly known as "glue ear") in children. Otitis media is an inflammation of the inner ear that often leads to an accumulation of fluid in the inner ear canal. Otitis media often appears as a complication of various viral and bacterial infections, including measles. If left undetected, otitis media can lead to hearing loss and learning disabilities. Authors of studies examining this issue have not formulated a widely accepted mechanism for how ETS might increase the risk of otitis media in children. There are two theories that are proposed but have not been scientifically proven: 1) One theory is that ETS somehow chronically irritates the eustachian tube of the inner ear, leading to the inflammation; and 2) The second theory is that ETS potentially increases the risk of upper respiratory tract infections that spread to the inner ear. The results of the studies on this subject are variable and are subject to the same confounders that potentially bias the results of studies on other ETS related issues. While the science on this issue is controversial, the reported seriousness of otitis media makes investigators anxious to make recommendations for child safety. However, the studies on otitis media and parental smoking have not established a clear association.

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RESULTS OF SELECTED STUDIES ON OTITIS MEDIA

- | | |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Said, et al., 1978 | Reported that number of tonsillectomies/adenoidec-tomies were related to the amount of parental smoking in the home |
| Pukander, et al., 1985 | Reported that parental smoking in the home increased the risk of acute otitis media and that breast-feeding seemed to have a protective effect |
| Kallail, et al., 1987 | Reported that parental smoking was not associated with the occurrence of otitis media |
| Zielhuis, 1989 | Reported that parental smoking was not related to an increased risk of otitis media |
| Strachan, 1990 | Reported that parental smoking was an important determinant of middle-ear underpressure and effusion |
| Strachan, 1989 | Reported that approximately one-third of the cases of middle ear effusion in their subjects were attributable to passive smoking |
| Taninio, et al., 1988 | Reported that parental smoking was more prevalent among the subjects with recurrent otitis media |
| Kraemer et al, 1983 | Reported that parental smoking, atopy, and catarrh posed the greatest risk to children of developing persistent middle-ear effusions when present together in the same child |

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Pukander, et al., 1990

Reported that maternal smoking increased the risk of acute otitis media in infants and especially of recurrent attacks

Vinther, et al., 1982

Reported that there were no effects of parental smoking on the frequency of otitis media in children

Moorhead, 1985

Reported that otitis media was found to be related to parental smoking in this general practice study

Black, 1985

Reported that parental smoking increased a child's risk of undergoing surgery for otitis media

Fleming, et al., 1987

Reported that full time day-care attendance increased the risk of ear infections (odds ratio = 3.8)

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Said, G., Zalokar, J., Lellouch, J., Patois, E. "Parental smoking related to adenoidectomy and tonsillectomy in children" Journal of Epidemiology and Community Health 32(2): 97-101, 1978.

The authors of this study investigated the histories of adenoidectomy and tonsillectomy and parental smoking habits for 3920 school children aged 10 to 20 years. The two surgical procedures were considered to be indexes of repeated upper respiratory tract disease in early childhood. The authors reported that both procedures were significantly related to the amount of smoking by each parent in this study. The authors claim that the relationships remained after they controlled for age, sex, day nursery attendance, sibship size, and history of appendectomy.

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Parental smoking related to adenoidectomy and tonsillectomy in children

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SUMMARY Histories of adenoidectomy and tonsillectomy were ascertained, as well as smoking habits of both parents, using questionnaires answered by 3920 schoolchildren aged 10 to 20. Adenoidectomy and/or tonsillectomy, considered as an index of repeated upper respiratory tract disease in early childhood, was very significantly related to the amount of smoking by each parent. This relationship persisted when age, sex, day nursery attendance, sibship size, and history of appendicectomy were controlled.

Introduction

An association between respiratory symptoms in children and the smoking habits of their parents has been found in several studies. Colley (1974) showed that the prevalence of cough in schoolchildren aged 6 to 14 was related to smoking by their parents. This relationship appeared to be indirect and cross-infection was an important element, as the prevalence was doubled among children whose parents had respiratory symptoms not associated with smoking. Colley *et al.* (1974) also found that the incidence of bronchitis and pneumonia among infants under one year of age was doubled when both parents smoked, whether or not the parents also had respiratory symptoms. Over the age of one year, the incidence was related only to parental respiratory symptoms.

Recently Lebowitz and Burrows (1976) have reported that persistent cough, phlegm, and wheezing in children under 15 were related to smoking habits of adults in their households, but not significantly so when similar respiratory symptoms in household adults were controlled. Harlap and Davies (1974) studied hospital admission rates during the first year of life of infants whose mothers' smoking habits were known. The babies of smoking mothers were more often admitted for bronchitis and pneumonia, but there was no significant difference in admission rates for upper respiratory tract infections. This negative result is in contrast with experimental findings that in animals placed in a smoke-filled atmosphere, a

large proportion of smoke particles are retained in the upper respiratory tract (Chretien *et al.*, 1973). However, as Harlap and Davies (1974) remarked, hospital admission rates are a poor indicator of the incidence of upper respiratory tract infections, which rarely require hospital treatment.

We present here the results of an investigation of the relationship between adenoidectomy and/or tonsillectomy in children, selected as an index of upper respiratory tract disease, and smoking by their parents.

Methods

Although the prevalence of upper respiratory tract disease is difficult to estimate directly, the child with repeated attacks is often, rightly or wrongly, subjected to adenoidectomy at about one year of age, and/or tonsillectomy at about five years of age. For this reason, we chose history of adenoidectomy and/or tonsillectomy (A or T) as an index of the prevalence of upper respiratory tract disease. Since these operations occur in early childhood, they precede any smoking by the child himself.

In 1975-76, students in nine secondary schools in Paris were given questionnaires to fill in by themselves in class. The questions covered sex; age; number of siblings; day nursery attendance before the age of three; smoking habits of mother (choices: non-smoker, 1 to 5, 6 to 10, 11 to 20, or more than 20 cigarettes a day) and father (choices: the same + pipe or cigars); and history of adenoidectomy, tonsillectomy, and appendicectomy. This last was

Table 1 Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by amount of smoking by each parent, as reported by their children

FATHERS							
Non-smokers	No. of cigarettes a day				Pipe and cigar only	ALL FATHERS	
	1-5	6-10	11-20	21+			
MOTHERS							
Non-smokers	28 (1550)	37 (412)	39 (380)	48 (305)	54 (175)	31 (157)	35 (2979)
Cigarettes a day							
1- 5	37 (110)	44 (123)	48 (87)	56 (62)	50 (42)	43 (58)	45 (482)
6-10	38 (74)	50 (34)	60 (83)	39 (38)	53 (19)	56 (18)	49 (266)
11+	51 (55)	47 (15)	58 (12)	67 (45)	48 (40)	58 (26)	53 (193)
ALL MOTHERS	30 (1789)	40 (584)	44 (562)	50 (450)	53 (276)	38 (259)	38 (3920)

¹ Test of significance of difference in % A or T by amount of smoking of fathers: $\chi^2 = 118.0$, 5 DF, $P < .001$

² Test of significance of difference in % A or T by amount of smoking of mothers: $\chi^2 = 63.0$, 3 DF, $P < .001$

intended as a control question. The children were not informed of the purpose of the questionnaire.

Less than 1% of the questionnaires lacked information on parents' smoking habits or on history of operations and these were rejected. The questionnaires of 3920 students (35.9% boys and 64.1% girls) aged 10 to 20 (except for 35 under the age of 10) were finally analysed. Information on number of siblings or sex was missing on 52 questionnaires (1.3%).

Very few children (56) reported that their mothers smoked more than 20 cigarettes a day, so they were grouped with those reporting maternal smoking of 11 to 20 cigarettes a day. Children whose fathers were reported to smoke both cigarettes and a pipe or cigars were grouped by paternal cigarette consumption, leaving a residual category of children whose fathers smoked a pipe or cigars only. The results were analysed using the χ^2 test with Yates' correction where appropriate.

Results

Table 1 shows the percentage of children reporting A or T, or both, grouped by the smoking habits of each parent. In the lower section of the Table it can be seen that the percentage of A or T increased very markedly with the quantity of cigarettes smoked by the mother, and very significantly also with the number smoked by the father. There is an intermediate value for the group whose fathers smoked a pipe or cigars only.

Table 2 Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by age and sex

Age	Boys	Girls	Total by age
< 15	40 (633)	36 (1308)	37 (1941)
15+	44 (766)	35 (1196)	38 (1962)
Total by sex:	42 (1399)	36 (2504)	

Difference between boys and girls significant at 0.1% level.
Difference between ages not significant overall or for either sex.

If the smoking habits of both parents are considered simultaneously, the frequency of A or T was higher when both parents smoked than when only one did, except when one parent was a heavy smoker. Thus, while 28% of the children with two non-smoking parents reported a history of A or T, calculations summarising Table 1 show that 42% of the children with one smoking parent, and 51% of the children with two smoking parents, reported such a history.

Boys reported A or T more frequently than girls (Table 2). Age differences were not significant. Children who had attended a day nursery also reported A or T more frequently than non-attenders (47% compared with 37%). The percentage of children reporting A or T decreased regularly overall from 47% of only children to 29% of those with three or more siblings (Table 3), but considered separately by sex and number of smoking parents (both these variables interact with family size),

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there was no general drop in percentage A or T until family size reached two or more siblings. Nevertheless, the strong relationship between parental smoking and history of A or T was found in both sexes and in all sibship sizes, irrespective of day nursery attendance, and in eight of the nine schools, drawing pupils from a variety of socio-economic strata. The association was not significant in the ninth school, where only 36 children took part.

A significant association was found between amount of maternal (but not paternal) smoking and percentage of appendicectomies (Table 4, totals). This was mainly due to the increased frequency of appendicectomy in children with a history of A or T (25%) compared to those without such a history (16%). But a weak association did remain between appendicectomies and amount of maternal smoking among children without a history of A or T. Appendicectomies were reported significantly more often in girls (20%) than boys (18%) but the slightly higher proportion of older children reporting this operation was only marginally significant and there was no relationship to number of siblings.

Discussion

Our study confirms the finding of an association between parental smoking and the prevalence of persistent upper respiratory tract disease in their children, as indicated by adenoidectomy or tonsillectomy. However, some points need further elucidation.

First, how valid are reports by those aged 10 to 20 of operations that may have occurred in the first few years of life? As a rule, children are aware of their past operations, partly because of the importance attached to these by their parents, and partly because of the many medical forms they will have filled in at school. The overall proportion reporting A or T (38%) seems to correspond to medical practice in the early 1960s. We note that the reporting of day nursery attendance, another event occurring before three years of age, followed the expected demographic pattern: it was most often reported among only children, and least often among those with three or more siblings.

The proportion (19%) reporting appendicectomy may appear surprisingly high in comparison with that

Table 3. Percentages (total numbers) of children reporting adenoidectomy and/or tonsillectomy by sex, number of siblings, and smoking habits of parents as reported by their children

No. of siblings	Boys			Girls			Total	Test of significance*	
	No. of smoking parents			No. of smoking parents				Boys	Girls
	0	1	2	0	1	2			
0	29 (69)	55 (96)	75 (36)	34 (97)	51 (120)	57 (46)	47 (464)	$\chi^2 = 22.2$ $P < .001$	$\chi^2 = 8.8$ $P < .02$
1	38 (180)	56 (131)	52 (93)	32 (280)	44 (248)	56 (135)	44 (1087)	$\chi^2 = 12.6$ $P < .005$	$\chi^2 = 21.9$ $P < .001$
2	34 (144)	44 (145)	55 (64)	27 (237)	39 (284)	50 (103)	38 (977)	$\chi^2 = 8.4$ $P < .02$	$\chi^2 = 17.8$ $P < .001$
3+	25 (162)	35 (180)	53 (62)	18 (353)	33 (428)	37 (155)	29 (1340)	$\chi^2 = 16.4$ $P < .001$	$\chi^2 = 31.2$ $P < .001$
Total	32 (535)	46 (572)	56 (255)	26 (967)	39 (1080)	48 (439)		$\chi^2 = 47.2$ $P < .001$	$\chi^2 = 76.0$ $P < .001$

*Test of significance of difference in % A or T by number of smoking parents: χ^2 with 2 DF

Table 4. Percentages (total numbers) of children reporting appendicectomy by amount of smoking of each parent and by whether or not they also reported A or T

Mothers		No. of cigarettes a day			Test of significance
A or T	Non-smoker	1-5	6-10	11+	
No.	15 (1951)	17 (264)	21 (136)	24 (87)	$\chi^2 = 8.7$ $P < .05$
Yes	24 (1028)	23 (218)	25 (130)	36 (106)	$\chi^2 = 7.4$ $P < .10$
Total	18 (2979)	20 (482)	23 (266)	31 (193)	$\chi^2 = 20.5$ DF = 3 $P < .001$

Fathers		No. of cigarettes a day				Pipe or cigars only	Test of significance
A or T	Non-smoker	1-5	6-10	11-20	21+		
No.	17 (1259)	13 (352)	15 (313)	18 (223)	20 (131)	12 (160)	$\chi^2 = 7.2$ $P > .20$
Yes	23 (530)	24 (232)	28 (249)	28 (227)	26 (145)	22 (99)	$\chi^2 = 3.7$ $P > .50$
Total	19 (1789)	17 (584)	20 (562)	23 (450)	23 (276)	16 (259)	$\chi^2 = 11.0$ DF = 5 $P < .06$

in English-speaking countries. In French medical practice, appendicectomy can be considered as an index of the incidence of acute abdominal conditions rather than appendicitis. In fact, since all doubtful cases are resolved in favour of appendicectomy, a perforated appendix is rarely seen here. The fact that more girls than boys reported appendicectomy accords with the preponderance of girls among older children with recurrent abdominal pain (Dodge, 1976).

The strong association between history of A or T and appendicectomy may have been due to several factors. There is, firstly, the possibility that some children answered positively (or negatively) to all three questions about operations; but the fact that appendicectomies showed a different demographic pattern than A or T tends to increase confidence in the validity of the self-reporting of operations by these schoolchildren. Then there is the positive association between social class and number of elective operations that has been found in the United States and Europe (Roos *et al.*, 1977; Wingerd and Sponzilli, 1977). Furthermore, independent of social class, there may be 'operation prone' children, at the mercy of their parents' or family doctors' predilections. On the other hand, some proportion of children presenting with acute abdominal conditions do in fact have upper respiratory infections (British Medical Journal, 1976; Dodge, 1976; Jones, 1976).

Secondly, how valid is information about parental smoking provided by those aged 10 to 20, and how are present smoking habits related to those of perhaps 15 years ago at the time of the A or T? The proportions of children reporting both parents non-smokers (40%), one parent smoking (42%), and both parents smoking (18%) were consistently the same for both sexes and for all age groups. Compared with a study of Paris policemen aged 46 to 52 (Zalokar *et al.*, 1974), less smoking by fathers was reported, but compared with a study of pregnant women in Paris (Schwartz *et al.*, 1972), more smoking by mothers was reported. Smoking by men in France is negatively related to social class and the proportion of men who stop smoking increases after the age of 45. By contrast, smoking by pregnant women is positively related to social class. Judging from the present study, maternal smoking may increase with age. It must be noted, however, that changes in parental smoking habits after the epoch of A or T would lead to an underestimation of the relationship of these variables.

More seriously, it is possible that the children who reported A or T or appendicectomy were more inclined to over-report parental smoking in spite of not knowing the purpose of the questionnaire.

(Bias can also occur in the opposite direction when parents are asked about their own smoking habits in conjunction with their children's symptoms). This was the reason for our question about appendicectomy; we thought *a priori* that it would not be associated with parental smoking.

However, the weaker association between maternal smoking and appendicectomy, even if it is due to this type of bias, cannot explain the much stronger association between A or T and parental smoking which remained among children not reporting appendicectomy. The most likely explanation for the association of appendicectomy with maternal smoking is that both increase with the rising socio-economic status of the family. Also, since appendicectomy is generally performed at a later age than A or T, it may be more closely related to present maternal smoking habits.

Even so, social class cannot be considered an important intervening variable in the relationship between parental smoking and A or T, since, as we have noted above, the social class gradients of smoking habits for men and women in France tend to run in opposite directions, yet the smoking habits of each parent are very significantly related to A or T in their children.

Reprints from J. Zalokar, U. 169, Institut National de la Santé et de la Recherche Médicale, 16 bis, Avenue Paul Vaillant-Couturier, 94800 Villejuif, France.

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Vinther, B., Elbrond, O., Pedersen, C.B. "Otitis Media In Childhood, Socio-Medical Aspects With Special Reference To Day-Care And Housing Conditions" Acta Otolaryngol 386(Supplement): 121-123, 1982.

This study was designed to determine the influence of day-care attendance and housing condition on the frequency of otitis media in childhood. Six hundred and eighty-one children, aged 3 to 4 years, were studied by taking somatic and social history, otological examination and tympanometry. The investigators found that earlier otitis media was 25% higher among children cared for outside home than among those cared for at home. Among the children attending day-care, there was also a statistically significant higher number of flat tympanometric curves and adenoidectomies. There were also statistically significant more children living in flats who had otitis media than there were children from houses. The children living in flats had a significantly higher number of adenoidectomies, but there was no difference between the children living in flats or homes in the number of flat tympanometric curves. The analysis showed that there were no effects of parental smoking or social status on the frequency of otitis media, adenotomy or tympanometric findings.

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OTITIS MEDIA IN CHILDHOOD. SOCIO-MEDICAL ASPECTS WITH SPECIAL REFERENCE TO DAY-CARE AND HOUSING CONDITIONS

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Abstract. In order to elucidate the influence of day-care and housing condition on the frequency of otitis media, 681 children, 3—4 years old, were investigated by taking somatic and social history, otological examination and tympanometry.

At the time of investigation 76 % of the children were cared for outside their home and one third was taken care of outside their home at the age of 3 months.

Among the children cared for outside home the history of earlier otitis media was 25 % higher than among those at home; at the same time there were statistically significant more flat tympanometric curves and adenoidectomies.

Regarding housing condition there were statistically significant more children with acute otitis media in flats than in houses, especially in newer concrete flats built after 1960, and there were significantly more adenoidectomies in those flats.

Tympanometry revealed no difference in respect to housing condition.

With a view to the elucidation of the incidence of otitis media in childhood and the relation of this problem to social factors, 681 children all 3—4 years old from the Aarhus district were studied.

METHOD

The children studied were divided into four groups as shown in Table 1. Of the series of 681 children, 336 were girls and 345 boys. The clinical study consisted in the taking of a thorough somatic and social history, including information on day-care and housing conditions and an otological examination including tympanometry.

Concerning day-care condition the question

asked focused on the time when the children first began to attend day-care nurseries, kindergarten or if they were cared for by a baby minder in a family day-care home. Concerning housing condition it was asked for if they lived in a flat or house, type of building material, number of rooms and construction year.

Table 1. *The number of children studied divided into four groups*

	No.
Randomly selected	287
Houses	119
Poor housing conditions	133
Concrete apartments	142
Total	681

RESULTS

The frequency of children cared for outside their homes related to age is shown in Fig. 1. After 3 months one third is cared for outside home and at the age of 4 years 76 % is cared for outside home.

Of the children cared for outside home 60 % started primarily at a baby minder while 40 % primarily started in day nursery or kindergarten.

Among the children cared for outside home the history of earlier otitis media was 25 % higher than among those at home, respectively 40 % and 32 % (Fig. 2). Children who attended day-care outside home before the age

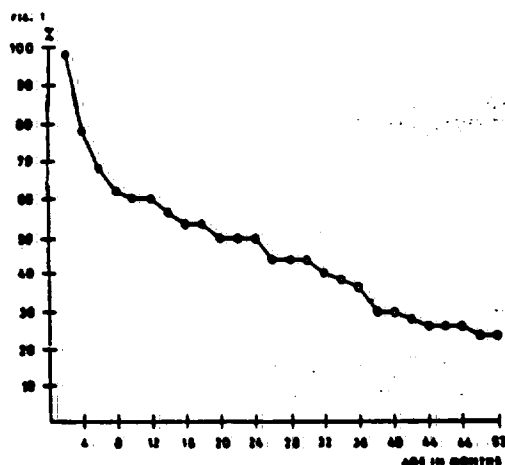


Fig. 1. Survival curve demonstrating age for first day-care outside home.

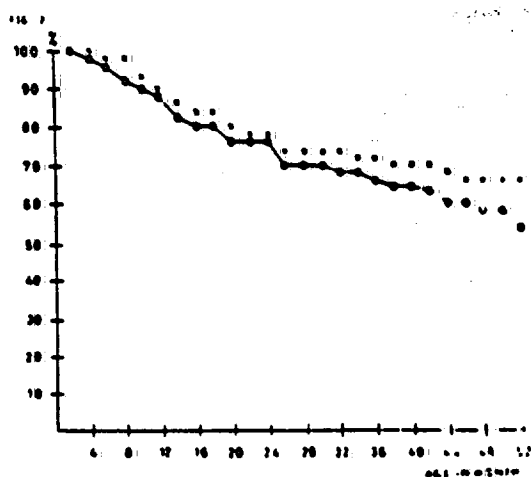


Fig. 2. Survival curve for first acute otitis media related to: day-care at home (x—x) and day-care outside home (o—o).

of 6 months had statistically significant more otitis media than children at home ($p < 0.05$). There were more boys than girls with a history of earlier otitis media and there were statistically significant ($p < 0.05$) more boys with ear discharge.

Children with earlier otitis media had an average of 2.7 attacks each and 97 % of these were treated with penicillin.

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Tympanometry revealed that there were statistically significant ($p < 0.05$) more children with flat tympanometric curves (Type B) among children attending day-care than among children at home (Table II).

Table II. Tympanometric findings (no. of ears) related to type of day-care

	Outside home		At home	
	N	%	N	%
Normal pressure (Type A curves)	571	99	223	65
Flat curves (Type B curves)	148	15	26	8
Negative pressure (Type C curves)	252	26	93	29

Adenotomy is most commonly performed in patients with chronic infection of the nasopharynx. 14 % of the children attending day-care outside home had undergone adenotomy versus only 7 % among the home-cared children (difference statistically significant $p < 0.01$).

There was statistically significant ($p < 0.01$) sex difference in the children who underwent adenotomy since there were only 30 girls versus 55 boys.

According to housing conditions there was statistically significant more children with otitis media living in flats than in houses, and especially was there a higher otitis media frequency in flats built after 1960 (Table III). The study revealed the same tendency for adenotomy (Table IV).

The tympanometric findings showed no difference in the occurrence of secretory otitis media in the four different housing conditions.

Table III. Number of 3—4 year old children with previous otitis media classified in houses/flats built before and after 1960

	Before 1960		After 1960	
	N	%	N	%
Houses	21/62	34	78/237	33
Flats	72/190	38	87/187	47

Table IV. Number of 3—4 year old children with previous adenoidectomy classified in houses/flats built before and after 1960

	Before 1960		After 1960	
	N	%	N	%
Houses	3/59	5	16/237	7
Flats	25/189	13	42/185	23

Looking at the housing condition and type of day-care at the same time (Table V) you find — as expected — that the best constellation with respect to low incidence of otitis media is care at home and living in an older house, and the worst is day-care outside home and living in a newly built flat.

The analysis shows that the social status and the smoking habits of the parents do not have any influence on the frequency of otitis media, adenotomy or the tympanometric findings.

Table V. Number of 3—4 year old children with previous otitis media classified in houses/flats and type of day-care

	Houses		Flats	
	N	%	N	%
At home	23/88	26	32/84	38
Outside home	76/211	36	127/293	43

DISCUSSION

Among the factors which have influence on the frequency of otitis media we have pointed out type of day-care and housing condition.

The reason for a greater amount of morbidity for children cared for outside home is presumably a consequence of higher frequency of upper respiratory infections in day-care centers (Strangert, 1976).

The change in life style, where now more than three third of all children are cared for

outside home, is probably the reason why otitis media occurs earlier in life than before (Platt, 1957).

Our statistical analysis has shown that the increased morbidity in newly built flats can not be explained from type of day-care, social status, smoking habits or sex. The four types of housing conditions are also fully comparable to the number of working hours the mother is spending outside home. It must therefore be assumed that the four groups of children are comparable and that the higher frequency of otitis media and adenotomy among children may be due to a factor inherent in newly built flats.

Of the flats built after 1960, 92 % were constructed of concrete, versus only 9 % before 1960. The higher frequency of otitis media and adenotomy in younger children might be due to a change in indoor climate caused by increased insulation and/or change of building materials — our investigation has not clarified this question (WHO-Report, 1979).

The above observations on the importance of day-care and housing conditions on morbidity are so interesting that they should encourage further research on the influence of indoor climate on health conditions — not least in children.

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Kraemer, M.J., Richardson, M.A., Weiss, N.S., Furukawa, C.T., Shapiro, G.G., Pierson, W.E., Bierman, C.W. "Risk Factors for Persistent Middle-Ear Effusions: Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy" Journal of the American Medical Association 249(8): 1022-1025, 1983.

SUMMARY: To ascertain risk factors for persistent middle-ear effusions (PMEE), we interviewed the parents of two groups of children. The first consisted of 76 children with PMEE who were admitted to the hospital for tympanostomytube insertion. The second, a control group, consisted of 76 children admitted for other types of surgery, who were matched for age, sex, season, and surgical ward. Nearly all (97%) of the children admitted for insertion of tympanostomy tubes had one or more episodes of suppurative otitis media. Only 59% of the control children had previous ear infections. Frequent ear infections sharply increased the risk for persistent effusions. Catarrh, household cigarette smoke exposure, and atopy also occurred more frequently in children with PMEE. The risk for middle-ear effusions was greatest when these three factors were all present. The avoidance of daily exposure to domestic tobacco smoke and, if atopic, of specific allergens should be included in the medical treatment of children with PMEE.

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Original Contributions

Risk Factors for Persistent Middle-Ear Effusions

Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy

Michael J. Kraemer, MD; Mark A. Richardson, MD; Noel S. Weiss, MD, DrPH; Clifton T. Furukawa, MD; Gail G. Shapiro, MD; William E. Pierson, MD; C. Warren Bierman, MD

• To ascertain risk factors for persistent middle-ear effusions (PMEE), we interviewed the parents of two groups of children. The first consisted of 76 children with PMEE who were admitted to the hospital for tympanostomy-tube insertion. The second, a control group, consisted of 76 children admitted for other types of surgery, who were matched for age, sex, season, and surgical ward. Nearly all (97%) of the children admitted for insertion of tympanostomy tubes had one or more episodes of suppurative otitis media. Only 59% of the control children had previous ear infections. Frequent ear infections sharply increased the risk for persistent effusions. Catarrh, household cigarette smoke exposure, and atopy also occurred more frequently in children with PMEE. The risk for middle-ear effusions was greatest when these three factors were all present. The avoidance of daily exposure to domestic tobacco smoke and, if atopic, of specific allergens should be included in the medical treatment of children with PMEE.

(JAMA 1983;249:1022-1025)

MIDDLE-EAR effusions are common in children, particularly after a suppurative middle-ear infection.^{1,2} Most effusions resolve after several weeks, but some persist relentlessly,^{3,4} causing hearing loss⁵ and associated language, behavioral, and learning deficits.^{6,7} Each year in the United States, an estimated 1 million operations take place in which tympanostomy tubes are inserted for persistent middle-ear effusions (PMEE).⁸

Several factors may affect the frequency of middle-ear disease: age,^{9,10}

sex,^{11,12} season,⁴ socioeconomic class,¹³ exposure to other children,¹⁴ catarrh,^{15,16} positional feeding styles,¹⁷ atopy,^{18,19} and a family history of ear disease.² In this study, we examined the association of these factors with the persistence of middle-ear effusions.

METHODS

The Research Committee and the Human Rights Committee at the Children's Orthopedic Hospital and Medical Center, Seattle, reviewed and approved these procedures. All parents gave informed consent before interview.

Case Selection

From June through October 1981, two general pediatric otolaryngologists performed 96 bilateral myringotomy and

tympanostomy-tube insertions (BMT) for PMEE. Children were treated surgically if they had bilateral effusions (with pneumatic otomicroscopy and tympanometry) that did not resolve after eight or more weeks of medical therapy, and which produced a hearing loss of 25 dB or greater. These children were admitted to a short-stay ward at the Children's Orthopedic Hospital and Medical Center for surgery. Their parents were asked to participate in an interview about risk factors for ear disease. We interviewed 76 parents of the 96 patients with PMEE. Of the 96 patients' families, two were excluded because they did not speak English, and 18 could not be reached.

Control Selection

Twelve physicians (four general surgeons, one urologist, one ophthalmologist, two dental surgeons, and four cardiologists) allowed us to contact parents of their patients admitted during the same period to the same short-stay surgery ward. From this group of 202 children, control subjects were matched to PMEE cases by age (± 1 year), sex, and month of surgery. Ninety-five patients were matched initially, but 14 could not be contacted. Five interviews were excluded because of current middle-ear effusions or past ear surgery.

Clinical Characteristics of Cases and Control Subjects

Twenty-one patients with PMEE (21.6%) had previous bilateral tympanostomy-tube insertions (range, one to nine). Two patients with PMEE had Down's syndrome and two had cerebral palsy. In

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Reprints not available.

The 76 control children, the reasons for admission were inguinal hernia repair (30), cardiac catheterization (17), biopsy or foreign-body removal (eight), umbilical, epigastric, or diaphragmatic hernia repair (six), orchiopexy (six), hydrocele repair (three), dental caries debridement (three), cystoscopy (one), esotropia repair (one), and proctoscopy (one). Down's syndrome occurred in only one control child who had cyanotic congenital heart disease. No other medical condition occurred more than once in either group.

Interview

Parents were interviewed within eight weeks of the scheduled surgery for the following information: (1) racial background, (2) family size, (3) health insurance status, (4) infant care and feeding practices, (5) household exposure to cigarette smoke, (6) frequency of suppurative otitis media (symptomatic ear infection treated with antibiotics), (7) frequency of catarrh (audible nasal breathing with rhinorrhea), (8) atopy (defined as one or more of the following disorders during the preceding 12 months: seasonal rhinitis [spring or summer sneezing, nasal itching, rhinorrhea, and nasal congestion]; asthma [recurrent wheezing, which improved with use of bronchodilators]; eczema [recurrent pruritic dermatitis, which improved with topical steroid therapy]), (9) family history of atopy, and (10) family history of significant middle-ear disease (six or more episodes of suppurative otitis media, or previous insertions of tympanostomy tubes).

Analysis

The likelihood of PMEE developing with a certain exposure was expressed as the relative risk and estimated using the Mantel-Haenszel method, standardizing for age (younger than 2 years, 2 years or older) and sex.¹⁰ Ninety-five percent confidence intervals for each relative risk estimate were derived using the method of Miettinen.¹¹ For some factors, the relative risk changed with increasing exposure. We used an extension of the Mantel-Haenszel method¹² to test for a linear trend of changing relative risk.

RESULTS

Table 1 shows the frequency and relative risk for each of the interview variables. Patients and control subjects were similar in all socioeconomic and demographic categories. There were no significant differences in birth weight, early feeding patterns, the use of nighttime bottles, or daily exposure to other children. Exposure to two or more household cigarette smokers increased the risk for PMEE.

Table 1.—Relative Risk of Persistent Middle-Ear Effusions (PME) According to Interview Variables

Characteristic	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*	95% Confidence Interval†
Demographic				
Sex				
M	46 (60.5)	46 (60.5)	1.0	...
F	31 (40.5)	31 (40.5)	1.0	...
Race				
White	66 (86.8)	66 (86.8)	1.0	...
Nonwhite	11 (14.5)	11 (14.5)	1.0	...
Household adults				
≥2	64 (84.2)	63 (82.9)	1.0	...
1	12 (15.8)	13 (17.1)	0.9	0.4-2.2
Bedding				
0	24 (31.6)	17 (22.4)	1.0	...
≥1	52 (68.4)	59 (77.6)	0.6	0.3-1.3
Health insurance				
Private	61 (80.1)	60 (78.7)	1.0	...
Nonprivate	15 (19.9)	16 (21.3)	1.4	0.6-2.6
Infant care‡				
Birth weight				
≥2,500	71 (93.4)	72 (94.7)	1.0	...
<2,500	5 (6.6)	4 (5.3)	1.3	0.3-6.0
First 6 mo				
Breast-fed only	23 (30.3)	21 (27.6)	1.0	...
Formula-fed only	23 (30.3)	26 (34.3)	1.1	0.5-2.7
Nighttime bottles (first 12 mo)				
Never used	47 (61.8)	52 (68.4)	1.0	...
≥5 nights per week	23 (30.3)	21 (27.7)	1.3	0.6-2.4
Daily exposure to other small children§				
None	37 (48.7)	36 (47.4)	1.0	...
At home only	14 (18.4)	10 (13.2)	1.4	0.5-3.6
At home and away	25 (32.9)	30 (39.4)	0.6	0.4-1.0
Irritant exposure				
Household cigarette smokers				
0	36 (47.4)	46 (60.5)	1.0	...
1	19 (25.0)	23 (30.3)	1.0	0.5-2.1
≥2	19 (25.0)	7 (9.2)	3.0	1.1-7.0
Household cigarette use,§ packs per day				
None	36 (47.4)	46 (60.5)	1.0	...
0.1-0.9	11 (14.5)	7 (9.2)	1.0	0.7-5.3
1.0-1.9	13 (17.1)	14 (18.4)	1.1	0.6-2.0
2.0-2.9	7 (9.2)	6 (7.9)	1.0	0.3-3.1
≥3.0	7 (9.2)	2 (2.6)	4.1	0.9-19.2
Otitis media				
Suppurative otitis media,§ episodes				
None	2 (2.6)	31 (40.8)	1.0	...
1-2	10 (13.2)	23 (30.3)	0.9	1.6-31.3
3-6	12 (15.8)	19 (25.0)	0.1	2.3-29.8
>6	52 (68.4)	33 (43.3)	106.7	46.4-987
Age at first otitis, mo				
≥6	36 (47.4)	33 (43.3)	1.0	...
<6	39 (51.5)	42 (55.7)	3.0	1.2-7.4
Family history of middle-ear disease				
Absent	42 (55.3)	53 (69.7)	1.0	...
Present	34 (44.7)	23 (30.3)	1.2	0.6-2.6
Nasal congestion (see text for definition)				
Frequency of symptoms,§ days monthly				
None	31 (40.8)	57 (75.0)	1.0	...
<5	10 (13.2)	6 (7.9)	3.6	1.0-8.8
6-15	16 (21.1)	6 (7.9)	4.0	1.7-12.8
>15	20 (26.3)	7 (9.2)	5.3	2.8-12.5
Atopic disease (see text for definition)				
Frequency of atopic symptoms,§ days monthly				
None	64 (71.0)	66 (86.8)	1.0	...
1-15	7 (9.2)	6 (7.9)	1.4	0.4-4.6
>15	15 (19.8)	6 (7.9)	3.7	1.2-10.6

Table 1.—Relative Risk of Persistent Middle-Ear Effusions (PMEE) According to Interview Variables (cont)				
Characteristic	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*	95% Confidence Interval†
Atopic disease (cont)				
Family history of atopic diseases				
Absent	26 (48.0)	36 (47.4)	1.0	...
Present	41 (54.0)	40 (52.8)	1.1	0.6-2.0

*Standardized for age and sex by the method of Mantel and Haenszel.¹⁰

†Approximate limits, calculated by the method of Miettinen.¹¹

‡Mean age \pm SD was 3.52 ± 2.7 years for the PMEE cases and 3.37 ± 2.6 years for control subjects. Mean birth weight \pm SD was $3,349 \pm 391$ g for PMEE cases and $3,335 \pm 359$ g for control subjects.

§Test for linear trend¹² comparing strata of increasing exposure (P=.NS).

¶Test for linear trend¹³ (P<.001).

‡‡Test for linear trend¹⁴ (P<.05).

Table 2.—Combined Effects of Risk Factors for Persistent Middle-Ear Effusions (PMEE)				
Attributes	No. (%) of PMEE Cases (N=76)	No. (%) of Surgical Control Subjects (N=76)	Relative Risk*†	95% Confidence Interval‡
None	10 (21.0)	31 (40.8)	1.0	...
Only 1 factor	29 (38.0)	23 (43.4)	1.8	0.7-3.6
Congestion (>1 day a month)	14 (18.4)	7 (9.2)	2.9	1.3-11.3
Smoking (>0.5 packs per day)	13 (17.1)	22 (28.9)	1.1	0.5-2.9
Atopy (>1 day a month)	1 (1.3)	4 (5.3)	0.6	0.06-4.6
2 factors combined	19 (25.0)	8 (10.5)	4.8	1.7-12.5
Smoking and congestion	11 (14.5)	5 (6.6)	4.3	1.3-13.9
Smoking and atopy	1 (1.3)	0 (0.0)
Congestion and atopy	7 (9.2)	3 (3.9)	4.5	1.1-18.7
All 3 combined	13 (17.2)	4 (5.3)	6.3	1.9-21.1

*Standardized for age and sex by the method of Mantel and Haenszel.¹⁰

†Test for linear trend comparing none, one, two, and three factors (P<.001).¹²

‡Approximate limits, calculated by the method of Miettinen.¹¹

nearly threefold. With household exposure to smoke from more than three packs of cigarettes per day, the risk increased fourfold.

Nearly all of the patients with PMEE had one or more previous episodes of suppurative otitis media. A significant trend of increasing relative risk occurred with increasing frequency of otitis media. When the first episode of otitis media occurred at younger than 6 months of age, there was an apparent threefold risk for PMEE. However, if the age at the first episode of otitis was standardized for the total number of episodes, the relative risk was only 1.6 (95% confidence interval, 0.6 to 4.5). Thus, early otitis media may increase the risk for more frequent episodes of suppurative otitis, but of itself does not significantly increase the risk for PMEE. A family history of ear dis-

ease increased the risk less than twofold, but despite this modest elevation, families with three or more affected members occurred only in the PMEE group.

Nasal congestion occurred more often, and was more persistent, in children with PMEE. With more persistent catarrh the risk increased from threefold to fivefold. Atopic diseases occurred twice as often in children with PMEE. In those who required repeated tympanostomy-tube insertion, ten (48%) of 21 had atopic disease. The risk for PMEE increased nearly fourfold in children with persistent atopic symptoms. A family history of atopic disease did not increase the risk for PMEE.

Table 2 shows the combined effects of nasal congestion, cigarette smoke exposure, and atopy. Nasal congestion alone elevated the risk nearly four-

fold. When cigarette smoke exposure or atopy was added to nasal congestion, the risk increased. Children with all three factors were more than six times as likely to manifest PMEE.

COMMENT

Suppurative otitis media, catarrh, household cigarette-smoke exposure, and atopy are important risk factors for the development of PMEE. The risk increases with more long-term exposure. Several clinical and laboratory studies would substantiate the importance of these factors. Recurrent infections can damage ciliary function and cause metaplastic changes in middle-ear mucous glands.² The altered mucosa secretes a thick, glue-like fluid, which is more likely to persist for long periods. Catarrh, which occurs more commonly in children with abnormal middle-ear pressures,¹³ may reflect repeated nasal infections, nasal irritant reactions, or nasal allergy. Each of these conditions could cause mucosal edema, hypersecretion, and abnormal ciliary function, which then results in obstruction or "dysfunction" of the eustachian tubes. Passive childhood cigarette smoke exposure increases the frequency of nonallergic respiratory symptoms¹⁴ and may aggravate respiratory allergies.¹⁵ In heavily exposed children, catarrh from infection or allergies could become more persistent. In children with atopic disease, allergic rhinitis is the likely cause of their increased risk of middle-ear effusions. Recent studies in patients with allergies have shown that nasal challenges with specific antigens can produce sustained abnormalities of eustachian tube function.¹⁶

Recurrent otitis media, nasal catarrh, cigarette smoke exposure, and nasal allergies chronically inflame the nasal and middle-ear cavities, causing persistent eustachian tube dysfunction. Middle-ear effusions will clear less readily in heavily exposed children, which may eventually necessitate surgical drainage and insertion of tympanostomy tubes. For these children, a medical treatment plan should include the elimination of tobacco smoke from the domestic environment and, if atopic disease is present, the control of specific environmental allergens.

This study was supported by a grant from the Children's Orthopedic Hospital and Medical Center Research Fund R2672, and by Associated Scientists to Help Minimize Asthma (ASTHMA) Inc, Seattle.

James Donaldson, MD, Barb Anderson, RN, and Donnie Lavery provided help in contacting patients. The physicians, surgeons, and support staff of the Children's Orthopedic Hospital and Medical Center, Seattle, provided assistance in contacting control subjects. Nancy Kraemer assisted in preparation of the manuscript.

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conditions of these patients were all maintained with placebo capsules for at least five to seven days during the withdrawal phase. While clear symptoms of withdrawal were observed, no severe reactions (eg, seizures or psychotic reactions) occurred. In keeping with our findings, few instances of severe withdrawal reactions associated with termination of clinically accepted doses of benzodiazepines have been reported in the literature. In the case reports cited by Drs Bargmann and Wolfe, the observations were made in uncontrolled conditions in which other factors may have been responsible for the reactions noted. In light of the widespread use of the benzodiazepine compounds, it is striking that so few instances of extreme withdrawal symptoms have been reported. However, more research, conducted under appropriately controlled conditions, is needed to evaluate this issue.

Drs Bargmann and Wolfe also raise questions about the efficacy of benzodiazepines in long-term use. Our recent report addresses this issue in only a preliminary manner. We are currently analyzing, for future publication, data from our study that support more directly the efficacy of long-term diazepam therapy.

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Risk Factors for Persistent Middle-Ear Effusions

To the Editor.—Kraemer et al¹ compared children with persistent middle-ear effusion (PMEE) admitted to a hospital for tympanostomy tube insertion with children admitted for other types of surgery and matched to patients with PMEE by age, sex, season, and surgical ward. Parents were interviewed about children's household exposure to cigarette smoke, frequency of nasal congestion, and frequency of defined atopic symptoms. The ratios of the proportions of children with PMEE to the proportions of children without PMEE in whom these factors were present were expressed as relative risks.

When relative risks were calculated individually for nasal congestion, cig-

arette smoke exposure (as measured by whether household residents reportedly smoked more than 0.5 packs per day), and atopy, nasal congestion was significantly different in children with and without PMEE, but cigarette smoke exposure and atopy were not. When risks were calculated for the three factors in pairs, exposure to cigarette smoke plus congestion and congestion plus atopy were significantly more frequently present in children with PMEE than in those without PMEE. Cigarette smoke exposure plus atopy could not be tested because of inadequate numbers of subjects. When all three factors were combined, the combination was significantly more frequent in children with PMEE than in those without PMEE.

Data derivable from the article's Table 2 show that when the influence of nasal congestion is controlled in the analysis of the influence of exposure to smoking on PMEE, the children exposed to smoking and those not exposed differed little in the proportion who had PMEE (Table).

Similar calculations show that, within the congestion and no-congestion groups, the proportions of atopic and nonatopic children who had PMEE were similar—74% and 68%, respectively, in those with congestion and 33% and 35%, respectively, in those without congestion.

Using other cutoff points and other measures of cigarette smoke exposure (Table 1), the authors found, in the small numbers of subjects with the highest levels of exposure, differences in relative risk between subjects with and without PMEE that were of borderline statistical significance, but they did not find a linear trend of increasing risk with increasing exposure.

The authors interpreted the analyses they reported as indicating that nasal congestion, cigarette smoke exposure, and atopy were all "important risk factors." We believe instead that the apparent associations between cigarette smoke exposure and PMEE, and between atopy and PMEE are probably artifactual and resulted (1) from combining, in the Table 2 analyses, cigarette smoke exposure and

atopy each with nasal congestion, which was strongly associated with PMEE, and (2) from not having separated, in the Table 1 analyses, smoking from nasal congestion, or atopy from nasal congestion.

We do not believe that evidence presented by Kraemer et al establishes either cigarette smoke exposure or atopy as risk factors for PMEE.

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1. Kraemer MJ, Richardson MA, Weiss NS, et al: Risk factors for persistent middle-ear effusions: Otitis media, rhinitis, cigarette smoke exposure, and atopy. *JAMA* 1983;249:1022-1025.

In Reply.—The letter by Rogers et al details their objections to our analysis of the risk factors for persistent middle ear effusions. They claim that because household cigarette smoke exposure and an atopic history seem to be strongly related to nasal congestion, which in turn is strongly related to PMEE, the apparent associations of PMEE with cigarette smoke exposures and atopy are only artifactual. They support their assertion by noting that, when the data from Table 2 are adjusted for the presence of nasal congestion, there is then no difference in the proportion of cases and controls who were atopic or exposed to cigarette smoke.

However, we believe that it is inappropriate to control for nasal congestion when assessing the risk for PMEE associated with exposures to household cigarette smoke and with atopy. This is because of our feeling that nasal congestion should not be considered as a confounder in this instance but rather as a means by which the adverse effect of atopy or smoke inhalation on the development of PMEE is mediated. If nasal congestion is not a determinant of household cigarette exposure or atopy but is actually a consequence of their actions, controlling for this variable will spuriously reduce the relative risk associated with cigarette smoke exposures and atopy by forcing cases and controls to be artificially similar with regard to these factors.

Thus, we contend that our original analysis was correct and that the results of our study support the hypothesis of an etiologic role for atopy and cigarette smoke exposure in the development of PMEE.

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Association Between Smoke Exposure, Nasal Congestion, and PMEEs*				
	Nasal Congestion Present		Nasal Congestion Absent	
	PMEE (%)	Control (%)	PMEE (%)	Control (%)
Smoke exposure	24 (73)	9 (27)	14 (39)	22 (61)
No smoke exposure	21 (68)	10 (32)	17 (33)	35 (67)

*PMEE indicates persistent middle-ear effusion.

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Black, Nick "The aetiology of glue ear-a case-control study"
International Journal of Pediatric Otorhinolaryngology 9: 121-
133, 1985.

This case-control study was designed to investigate the possible causes of glue ear (otitis media) in childhood. One hundred and fifty cases with two matched controls each made up the study population. Five factors were found to increase the risk of a child's undergoing surgery for glue ear: 1) parental smoking; 2) the child's mother being employed outside the home, but only if the father is employed in non-manual work; 3) attending pre-school day-care; 4) having an older sibling who had been diagnosed as suffering from glue ear; and 5) having been born locally. The author found that only one of these factors, parental smoking, appeared to be related to the actual development of glue ear. The other four factors were reportedly found to be related only to the chances of glue ear being detected in the child.

The children studied in this investigation were aged 4-9 years and had undergone a first operation for glue ear within the previous 30 months at the Radcliffe Infirmary in Oxford and was a resident of Oxford. The parents of these children were interviewed to obtain data on their child's medical, birth, family and social histories. Each of the cases was matched with two controls. One control was a child matched on age and sex who had attended a follow-up outpatient appointment in the general surgical or orthoptic departments. The second control was a child matched on age and sex from the same school class who was also the next child alphabetically of the same sex on the class roster.

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The aetiology of glue ear—a case-control study

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Key words: glue ear - etiology

Summary

A case-control study was carried out to investigate many of the proposed causes of glue ear in childhood. One hundred and fifty cases with two matched controls were found to be remarkably similar in nearly all medical and social aspects of their past and present lives, thus providing no support for many of the currently held views on the aetiology of glue ear. Of the 5 factors which were found to increase the risk of a child undergoing surgery for glue ear, only one of these is thought to be related to the development of the condition, rather than to the chances of its detection. This factor was parental smoking (RR 1.64). The 4 other risk factors appear to influence the chance of glue ear being detected, diagnosed and referred for surgical treatment - the child's mother being employed outside the home, but only if the father is employed in non-manual work (RR 3.0); attending pre-school day-care (RR 2.00); having an older sibling who had been diagnosed as suffering from glue ear (RR 1.84); and having been born locally (in Oxfordshire) (RR 1.89). Possible explanations for these social and behavioural factors are discussed.

Introduction

Glue ear (also known as serous or secretory otitis media) is a condition in which non-purulent fluid accumulates in the middle ear causing some conductive deafness. Children with glue ear often also suffer from recurrent attacks of acute otitis media (AOM). Although it is a widely held view that AOM may lead to glue ear [25,35],

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there is considerable evidence that glue ear predisposes to AOM [17,23]. Glue ear is currently the commonest reason for surgery during childhood [4], the peak ages in the UK being 5–8 years of age. Although the condition has been recognised since at least the middle of the nineteenth century, there is no general agreement as to its cause. There have, over the past one hundred years or more, been many aetiological theories which have been extensively reviewed elsewhere. The large number of diverse factors that have been considered means that further investigation of this subject is well suited to a case-control study design. The study described here attempts to examine many of the existing claims about aetiology, and to assess some previously unconsidered factors [6].

Amongst the existing claims are those with some scientific support (living in a damp, humid climate [38,40]; parental smoking [21]; being first born in a family [14]); some of indeterminate status (overcrowding [9,16,27,39]; low socioeconomic status [14,27,36]; day care attendance [14,36,39]; an allergic predisposition [7,12,14,18,28,39]); and some without support or as yet unevaluated (effects of heredity [10,39]; acute exanthemata [15,39]; infant feeding [3,13,21,30]; air travel [22,29,41]). New areas of interest considered are family characteristics (such as parental ages and work status; sexes of siblings); educational achievement of parents; ante-natal and delivery events; exposure to vaccines and X-rays; and contact with animals.

There are 3 other factors which have been suggested, the investigation of which is not suited to a case-control study design. These are air pollution [9,15]; as a consequence of the misuse of antibiotics for AOM [2,10,22,43,44]; and the failure to perform sufficient adenotonsillectomies in children [11,20,24,27,29,31,43]. Studies which have considered these theories have failed to provide any support for them [6].

Method

Study design

Between May 1981 and October 1982, the parents of each child aged 4–9 years who had undergone its first operation for glue ear within the previous 30 months in the ENT department, Radcliffe Infirmary, Oxford and was resident in Oxfordshire, were interviewed and asked about their child's medical, birth, family and social histories. For each case two controls were selected—the 'hospital' control from children attending a follow-up outpatient appointment in the general surgical or orthoptic departments (Table I) and the 'home' control from the same school class (the next child alphabetically, of the same sex). The controls matched the cases with respect to sex and age (hospital controls within 6 months; home controls within 12 months). The parents of cases and hospital controls were interviewed, using a structured questionnaire, by the author in the respective outpatient departments. Parents of home controls were interviewed by one or other of two research interviewers in the controls' own homes.

Surgery for glue ear was defined as myringotomy (with or without insertion of tympanostomy tubes) with or without adenoidectomy. The contents of the middle-ear

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TABLE I
DIAGNOSES IN 150 MATCHED HOSPITAL CONTROLS

Strabismus	57	Undescended testes & hydrocoele	20
Amblyopia	7	Phimosis	17
Hypermetropia/Myopia	6	Abdominal hernias	9
Reduced visual acuity	6	G.I.T./G.U. conditions	6
Refraction errors	6	Cysts, pilonidal sinus	5
Ptoxis	1	Others	10
	83		67

on operation were noted as 'dry', 'serous fluid' or 'glue'. Children with cleft-palate were excluded as this condition has been clearly shown to be associated with glue ear [33].

Subjects

The parents of only one potential case and 3 potential hospital controls declined to participate due to lack of time for the interview. The parents of potential home controls were approached for 146 of the cases (4 of the cases having left the District by that time). Of these, 13 (9%) declined to participate. A second potential control was successfully recruited in these instances. In two instances the potential home control's GP refused permission for inclusion in the study and another child from the same school class was obtained. Of the 146 controls finally identified and interviewed, four were withdrawn from the analysis as they had undergone surgery for glue ear.

The hospital controls were selected so that they would be comparable with cases as regards factors affecting health service usage, and the home controls for factors affecting accessibility and availability of services. Thus, if the frequency of a factor differs between cases and both sets of controls, this suggests the factor is specifically related to children undergoing surgery for glue ear. On the other hand, if the difference is only between cases and home controls (with no difference between cases and hospital controls), this suggests the factor is associated with children undergoing hospital care in general (and not specifically related to children with glue ear).

Statistical methods

The results are first presented as simple contingency tables that take no account of the matched design of the study. The two control groups are displayed separately because of the different selective biases operating on each. In addition, data obtained about the home controls are subject to information bias arising from the different interviewer and interview situation. Risk ratios for all variables were estimated (unmatched ratio of cross-products) and their significance tested (by computing a χ^2 value). Statistically significant variables ($P < 0.05$) were further examined to take account of possible confounding (using the Mantel-Haenszel method of stratification). The original data concerning these variables were re-

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analysed taking into account the matched study design. 95% confidence limits and significance testing (McNemar Test) for matched relative risks were computed.

Results

The respondents were mostly mothers (82%); of the remainder 5–6% were fathers, 11% were both parents, and 1% other relatives. There was no difference in this respect between cases and controls.

Of the 150 cases, 51 (34%) were aged 4 years–5 years 11 months; 69 (46%) 6 years–7 years 11 months; and 30 (20%) 8 years–9 years 11 months; 88 (59%) were male and 62 (41%) female. The age and sex distribution of this sample is similar to that for cases in the whole of Oxford Region (1975–1980). The same was true of the social class distribution (as determined by the father's occupation at the time of birth of the case).

Parents and siblings

The mean ages of both the fathers and the mothers of cases were similar to those

TABLE II
FAMILY MEMBERSHIP AND STRUCTURE OF CASES AND CONTROLS

	Cases	Hospital controls	Home controls
Parents' ages—Father *	36.5 ± 0.5	36.4 ± 0.6	36.6 ± 0.5
(mean ± S.E.M.)—Mother	32.5 ± 0.4	32.7 ± 0.4	33.5 ± 0.4
	No. (%)	No. (%)	No. (%)
Parental relationship **			
Together	143 (96)	135 (90)	130 (91)
Separated	7 (4)	15 (10)	12 (9)
Number of children			
1	9 (6)	18 (12)	9 (6)
2	84 (56)	80 (53)	82 (58)
3	40 (27)	39 (26)	33 (23)
4 or more	17 (11)	13 (9)	18 (13)
Birth order of subject			
1	63 (42)	69 (46)	58 (41)
2	67 (45)	57 (38)	55 (39)
3 and subs.	20 (13)	24 (16)	29 (20)
Sex of older siblings			
Male	62 (56)	52 (47)	59 (48)
Female	49 (44)	59 (53)	63 (52)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* The term 'father' is used to designate the male head of household and includes stepfather, and mother's common-law husband

** The term 'together' describes all instances of the subject having always lived with the same two adults (including subjects adopted at a young age). 'Separated' includes all others (e.g.) single parent families, step-parents etc.

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TABLE III

PARENTS' PAST AND PRESENT OCCUPATIONS⁶ AND COMBINATIONS OF PARENTAL WORKING STATUSES

NM, non-manual (Registrar General S.C.I. II, IIIN); M, manual (R.G.S.C. IIIM, IV,V).

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Occupation at birth of subject			
Father -NM	60 (41)	68 (46)	65 (48)
-M	85 (59)	79 (54)	70 (52)
Parental work combinations			
Father (NM) -mother working	33 (56)*	23 (37)	42 (60)
-mother not working	26 (44)	40 (63)	28 (40)
(M) -mother working	37 (47)	37 (49)	33 (49)
-mother not working	42 (53)	39 (51)	35 (51)

N.B. Differences not significant ($P < 0.05$) unless indicated.* $P < 0.05$ (comparison with hospital controls only)

of the parents of both sets of controls (Table II). A higher proportion of the older siblings of cases were male (though this was not statistically significant (n.s.)) and for all other measures of family structure only slight differences were observed. The length of parental full-time education and educational qualifications were remarkably similar between the 3 groups.

There was no significant difference between the proportions of fathers engaged in manual occupations (Table III). However, mothers of cases with work outside the home tended to be engaged in non-manual rather than manual work compared with the mothers of both controls. Any association with the working status of mothers was confined to the wives of non-manual men, and then only when compared with hospital controls ($P < 0.05$).

Preconception, pregnancy and perinatal events

Fewer of the parents of cases had used contraception during the year preceding the subjects' conception, though this difference was not significant. Apart from this observation, the preconception period for the 3 groups were similar. No differences were observed for antenatal events (raised B.P., anaemia, antepartum haemorrhage, influenza, rubella). Exposure during pregnancy to both medical factors (scans, drugs, X-rays and amniocentesis) and non-medical factors (smoking, food fads) was similar. Data on the place of delivery, type of delivery, gestation, birth-weight and admission to a special care baby unit were also similar for the 3 groups. Proportions of infants breast-fed and the duration of breast feeding showed little difference.

Childhood medical history and exposure to medical procedures

There were no significant differences between the groups in the proportion with a history of allergic manifestations or having contracted the common infectious

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TABLE IV

CHILDHOOD HISTORY OF ALLERGY, INFECTIOUS DISEASES AND EXPOSURE TO VACCINES, X-RAYS AND DAY-CARE

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Allergic conditions			
Infantile eczema	15 (10)	18 (12)	19 (13)
Hay fever	15 (10)	14 (9)	15 (11)
Asthma	7 (5)	4 (3)	3 (2)
Sensitivity to food/drugs	23 (15)	17 (11)	16 (11)
Infectious diseases			
Measles	34 (23)	39 (26)	28 (20)
Mumps	57 (39)	52 (35)	55 (39)
Chicken-pox	80 (54)	74 (50)	96 (68)
Rubella	45 (30)	51 (34)	36 (25)
Whooping cough	11 (7)	16 (11)	14 (10)
Immunizations			
All routine schedule	93 (63)	82 (55)	92 (65)
Pertussis	107 (71)	92 (61)	105 (74)
Measles	136 (91)	135 (90)	125 (88)
Additional non-schedule ¹	10 (7)	11 (7)	10 (7)
X-ray exposure			
Dental	11 (7)	13 (9)	N.A.
Head and neck	21 (14)	23 (15)	21 (15)
Day-care attendance ²			
nil or low	20 (13)	35 (23)	26 (18)
medium/high	130 (87) [*]	115 (77)	116 (82)

N.B. Differences not significant ($P < 0.05$) unless indicated.^{*} $P < 0.05$ (only compared with hospital control).¹ Additional tetanus, BCG, smallpox, TAB, cholera.² Day-care = (av. No. of hours per week \times No. of months attended).

diseases of childhood (Table IV). Exposure to the routine immunizations and to X-rays was also similar in the three groups. Comparison of the amount of pre-school day-care attendance showed cases had attended more than controls ($P < 0.05$ when compared with hospital controls).

ENT histories of parents and siblings

Parental history of having undergone tonsil and/or adenoid surgery showed remarkable similarity between the groups, with the proportion of mothers considerably higher than fathers (Table V). A higher proportion of the siblings of controls had a history of recurrent acute otitis media and recurrent tonsillitis ($P < 0.05$). In addition, if older siblings only are considered, a higher proportion of those of cases had a history of glue ear. The older siblings of cases with glue ear were more likely to have been referred to ENT departments and treated surgically, than the older siblings of controls, though this difference did not achieve statistical significance.

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TABLE V
ENT HISTORIES OF PARENTS AND SIBLINGS

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Parental history of Ts and As ¹			
Father	40 (28)	40 (29)	38 (27)
Mother	62 (42)	60 (40)	50 (36)
Sibling history of ENT problems	(n = 210)	(n = 208)	(n = 211)
Recurrent A.O.M. ²	42 (20) *	62 (30)	72 (34)
Recurrent tonsillitis	30 (14) *	45 (22)	41 (19)
Glue ear	26 (12)	16 (8)	17 (8)
Sibling treatment for glue ear	(n = 26)	(n = 16)	(n = 17)
Referral to ENT	22 (85)	12 (75)	12 (70)
Surgery	19 (73)	9 (56)	10 (59)
Older siblings history of ENT problems	(n = 84)	(n = 81)	(n = 84)
Recurrent A.O.M.	19 (23) *	31 (38)	33 (39)
Recurrent tonsillitis	19 (23) *	34 (42)	29 (35)
Glue ear	19 (23) **	8 (10)	14 (17)
Older siblings treatment for glue ear	(n = 19)	(n = 8)	(n = 14)
Referral to ENT	18 (95)	5 (63)	9 (64)
Surgery	16 (84)	5 (63)	8 (57)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* $P < 0.05$ (compared with hospital and home controls).

** $P < 0.05$ (compared with hospital control only).

¹ Tonsillectomy and adenoidectomy.

² Acute otitis media.

Home environment

Most aspects of housing conditions showed great similarity. These included the type and age of the accommodation, the occupying basis (owned, rented, tied), density of occupation and the basic amenities (bath/shower, washing machine, telephone, refrigerator). The exception to this was that a higher proportion of case

TABLE VI
FAMILY MOBILITY DURING SUBJECT'S LIFETIME

	No. (%) of cases	No. (%) of hospital controls	No. (%) of home controls
Residence at time of subject's birth			
Oxfordshire	123 (82) *	107 (71)	106 (75)
Elsewhere	27 (18)	43 (29)	36 (25)

N.B. Differences not significant ($P < 0.05$) unless indicated.

* $P < 0.05$ (only compared with hospital controls).

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families reported using an 'unsealed' heating system, that is, a system that emits the products of combustion (open fires, gas fires, paraffin stoves) ($P < 0.05$).

A higher proportion of the families of cases were already living in Oxfordshire when the subject was born, than was true for the controls ($P < 0.05$) (Table VI). Other measures of geographical mobility showed no difference. Other factors examined which also showed no difference included air travel by the subjects, possession of pets, and regular contact or close proximity to farm animals.

Smoking habits of household members

The present smoking status of the parents (smoker, ex-smoker, never-smoked) showed a small and insignificant difference between cases and controls. A smoking rate was calculated based on the number of years of the subjects life that the household member had smoked for, and the daily number of cigarettes smoked (or cigarette equivalent in the case of cigar and pipe smokers). This revealed that a slightly higher proportion of cases had been exposed to medium/high levels of smoking than had controls, but this difference failed to achieve statistical significance.

Confounding and matched analysis

The relative risks (RR) for all variables included in Tables II-VI were estimated by comparison with hospital controls and with home controls. For all but one variable the R.R. based on comparison with the hospital control was similar to that based on comparison with the home control (the exception was the effect of the mother working outside the home). Variables with RRs which proved to be statistically significant ($P < 0.05$), plus that for parental smoking habits, are shown in Table VII. These variables were further examined for evidence of confounding. The

TABLE VII

RELATIVE RISKS OF GLUE EAR BASED ON UNMATCHED COMPARISON WITH HOSPITAL CONTROLS^a, AND HOME CONTROLS^b

Variable	R.R. ^a	R.R. ^b
Working mother	1.41	0.89
with N.M. father	2.16 *	0.85
Day-care attendance		
medium/high	2.00 *	1.47
Siblings with glue ear		
older siblings only	2.54 *	1.81
Smoking rate		
household	1.45	1.28
Residence		
born in Oxon	1.86 *	1.52
Unsealed heating system	1.59 *	1.59 *

N.B. Differences not significant ($P < 0.05$) unless indicated.

* $P < 0.05$.

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TABLE VIII

RELATIVE RISKS OF GLUE EAR BASED ON MATCHED COMPARISON WITH HOSPITAL CONTROLS ^a, AND HOME CONTROLS ^b

Variable	R.R. ^a	95% conf. limits	R.R. ^b	95% conf. limits
Working mother	1.36	—	0.94	—
with N.M. father	3.00 *	1.15-7.80	0.89	—
Day-care attendance (med/high)	2.00 *	1.13-3.53	1.50	—
Older siblings with glue ear	1.84 *	1.01-3.37	1.64 *	1.06-2.55
Smoking rate household	1.64 *	1.03-2.61	1.52 *	1.06-2.21
Residence born in Oxon	1.89 *	1.11-3.21	1.88 *	1.07-3.29

N.B. Relative risks not significant ($P < 0.05$) unless indicated.* $P < 0.05$; * $P < 0.02$; (McNemar test).

only factor for which the estimate of RR was the result of confounding was unsealed heating (when parental smoking and birth in Oxfordshire were taken into account).

The other variables were re-examined by matched-pair analysis (Table VIII). This revealed similar findings to those from unmatched analysis (Table VII) for cases and both sets of controls, apart from parental smoking, for which the RR became significant on matched analysis. The data were further analysed on the basis of the contents of the middle-ear as found at operation. Of the 150 cases, 106 were found to have thick mucoid 'glue' in at least one ear, whilst the remaining 44 had either thin serous fluid or no fluid at all. Estimates of relative risk based on matched analysis of only those with 'glue' revealed similar findings to analysis of the complete series.

Discussion

The main methodological problem encountered was the selection of controls. There was no ideal group of hospital patients from which to choose—those selected were the most appropriate available. As regards home controls, possible bias arising from different interviewers in a different setting from cases and hospital controls is considered to have had only an insignificant effect. This can be judged by the similarity of the relative risks obtained by comparison with each set of controls.

The size of this study means that risk factors present in 50% of controls would have a 90% chance of being detected if the relative risk associated with them was at least 2.0. However, the relative risk would have to be at least 3.5 if the factor was present in only 5% of controls. Negative findings must be interpreted in this context. The most striking finding was the similarity between cases and controls, or, to put it another way, how remarkably ordinary children with glue ear appeared to be in

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nearly all aspects of their past and present lives. There were, however, a few exceptions.

(a) Climate

Evidence for the effect of humidity and altitude is difficult to obtain in a localised study of this design. Oxfordshire has a local reputation as having a high prevalence of glue ear attributed to the effect of the Thames Valley; and indeed, cases were found to be associated with having been born in Oxfordshire (RR 1.89; $P < 0.02$). While local climatic conditions could be responsible for such a finding, many other environmental factors could also be implicated.

(b) Socio-economic conditions

Previous studies of the influence of social class have failed to demonstrate any association with glue ear [27,34,36,39,42]. This was true of this study. There is, however, no reference in the literature to the influence of mothers working outside the home, a factor that appeared to be associated with glue ear (Table VIII), compared to hospital controls, if the father was employed in non-manual work (RR 3.0; $P < 0.05$). However, this association with mother's employment status was not observed in comparison with home controls. There are 3 possible explanations for this difference—the association is due to chance; the risk estimate from the hospital control analysis may reflect a relative 'lack' of occupation outside the home for control mothers rather than an 'excess' for case mothers; or, information bias associated with the home interview may have led to 'over-recording' of maternal occupations by the mothers of home controls. It is not apparent from the data which of these explanations is correct. The only related information, on parental education, showed no associations with glue ear in the child.

A possible explanation for the association between glue ear and maternal employment status, where the father is employed in non-manual work, may be the family's attitude to the mother working. Wives of non-manual husbands are perhaps less likely to work for primarily financial reasons than the wives of manual men. Working for other reasons (e.g. career oriented; psychological benefits of getting out of the home) may be associated with attitudes to health and illness that differ from the attitudes of non-manual families in which the mother does not work. In turn these attitudes may be associated with the detection of glue ear and obtaining surgical treatment. In other words, the risk associated with mothers working may be explained in terms of health behaviour, rather than in terms of disease aetiology. Investigation of the effect of housing conditions has produced conflicting results in the past [9,15,16,39]. There was no clear evidence of housing conditions influencing the occurrence of glue ear in this study.

(c) Family history

It is difficult to obtain reliable information on the history of glue ear in parents due to the frequent changes of name the condition has undergone. If parents had suffered from glue ear, severely enough to necessitate surgery, then they would, on average, have been treated in the 1940s. At this time surgical treatment would have

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involved adeno-tonsillectomy. There was no difference in the history of this operation between case and control parents (Table V).

The siblings of cases were more likely to have been diagnosed as suffering from glue ear than the siblings of controls (RR 1.84; $P < 0.05$). Conversely, a history of recurrent acute otitis media (AOM) was commoner in the siblings of controls. If these two middle-ear conditions are considered together, then any association between middle-ear disease in siblings and glue ear in the subject disappears (RR 0.77). Whilst not all children with a history of recurrent AOM have glue ear, the clinical distinction between the two is often not clear [17,23,25,35]. The initial diagnosis of glue ear is usually made by a General Practitioner, who, in negotiation with the parents, decides whether or not to refer the child for specialist attention. With over 200 GPs referring to the ENT department in this study, it would be expected that a wide range of indications for referral were being practiced. In this way, a child with a sibling with glue ear would be more likely to also be diagnosed as glue ear (rather than recurrent AOM) than a child without a 'glue ear' sibling (assuming all children from the same family attend the same GP with the same parents). This is supported by the finding that siblings of cases diagnosed as having glue ear are more likely to be referred to ENT care and be managed surgically than siblings of controls (Table V).

The risk associated with a sibling with glue ear therefore appears to be a product of the behaviour of parents and health care professionals, rather than any 'true' hereditary effect, though this requires further investigation. This is consistent with the only recently published study which has examined this factor [39].

(d) Subjects medical history

No association was found between any aspects of the subject's past medical history and the occurrence of glue ear. These aspects included infant feeding, common infectious diseases and allergic conditions. This study confirms the findings of several others that demonstrated the proportion of glue ear cases with a history of allergy was similar to the prevailing frequency in the general population [8,19,26,38].

(e) Behaviour

A significant association was found (RR 1.64; $P < 0.05$) between glue ear and the smoking habits of all household members throughout the subject's life. This analysis assumes a constant level of exposure to smoke throughout the subject's life. Further study would be required to determine whether or not the risk of smoke is associated with any particular stage of childhood. This finding is consistent with a recent study in the USA [21] and other evidence about the hazards of passive smoking [1].

The reported risks of exposure to pre-school day-care have been conflicting [3,14,39]. This study suggests day-care attendance is a risk (RR 2.00; $P < 0.02$), though the mechanism is unclear. Day-care may increase the likelihood of a child acquiring a middle-ear infection and subsequently being examined for evidence of glue ear, or the day-care staff may be on the lookout for evidence of glue ear and proceed to alert unsuspecting parents.

In conclusion, while this study has failed to substantiate the role of many

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biological factors in the aetiology of glue ear (with the exception of tobacco smoke), it has suggested that social and behavioural factors may be at least as, if not more, important in determining which children are detected, diagnosed and treated surgically for glue ear. The influence of such factors requires further investigation to support such a claim.

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Moorhead, Robert "Passive smoking and young children's health"
Australian Family Physician 14(10): 1058-1062, 1985.

This article is based on a general practice study. The aim of this study was to determine whether the children of smoking parents in this population have different morbidity patterns in their visits to a general practitioner. The eighteen month investigation examined the families of 170 children from 0-5 years of age. Families were matched for age, sex, social class and size. The author reports that the smoking group children "attended more frequently, had more diagnoses per consultation and spent more days in hospital" than the non-smoking group children. The diseases that were reportedly associated with parental smoking in this study were otitis media, upper and lower respiratory disease, conjunctivitis, infectious disease and accidents. There were several conditions which were found not to be associated with parental smoking in this study such as croup, skin disease, rubella, and modified pertusis.

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Passive smoking and young children's health

Robert Moorhead

Recent international studies have been documented which suggest a link between passive smoking and disease in young children. They include studies of passive smoking and its relationship to pneumonia and bronchitis,^{1,2} respiratory disease,³ restricted activity due to acute respiratory disease,⁴ increased winter admissions⁵ and increased visits to doctors.⁶ This article is based on a general practice study in this area.

The aim of this study was to see if children of smoking parents have different morbidity patterns in their visits to a general practitioner. The 24 categories of health problems studied are as follows:

- Total consultations
- Total diagnoses (all diagnoses were by encounter)
- Winter consultations
- Spring consultations
- Summer consultations
- Autumn consultations
- Respiratory diagnoses
- Preventive classification diagnosis
- Nervous and sense organ diagnoses
- Skin diagnoses
- Trauma diagnoses



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- Upper respiratory tract infection and pharyngitis
- Tonsillitis diagnoses
- Wheezing — patient initiated diagnoses
- Wheezing — total diagnoses
- Vaccinations
- Gastroenteritis diagnoses
- Rubella diagnoses
- Scarlet fever diagnoses
- Modified pertussis diagnoses
- Conjunctivitis diagnoses
- Otitis media diagnoses
- Hospital admission — number of days
- Infectious disease diagnoses.

The study began on 1 January 1979 and ran for 18 months. Regular attenders of the author's practice were selected because some families used more than one doctor. This ensured that subsequent morbidity was being presented to the recorder only. All practice records were studied and families were selected, with married parents (under 45 years of age), in which every member had attended the practice at least once in the past two years. From this group of families 170 children, from newborn to the age of five years, were identified. Their parents' smoking habits had been recorded previously and the children were divided into two groups: one or both parents smoking; or neither smoking.

Families were matched for age, sex, social class⁷ and size (greater than two, or two or less children) using punch cards. As with all matching procedures, not all children could be matched so the study started with 106 children — 53 in each group. This was a non randomised cohort study.

The morbidity recorded fulfilled the definitions in the International Classification of Health Problems in Primary Care (ICHPPC).⁸ The diagnoses were studied according to age group.

The practice after hours work is performed by a locum service run by the principals and a written report was available on such diagnoses. All in-

patient hospital records for patients in this survey were studied by the author and the number of days in hospital recorded. Home visits, after hours visits and consultations were included in the survey.

There were two outcomes measured in the study. One was the chi-square on the 24 items of morbidity for both groups, which was calculated by computer. The other was the mean of the diagnoses for the smoking and non smoking group.

The smoking group children attended more frequently, had more diagnoses per consultation and spent more days in hospital.

Table 1 shows the common diagnoses for the two groups and the predominance in the smoking group for certain diagnoses. In Table 2 less common diagnoses and other health problems are recorded. There was a similar finding for total wheezing (initial and doctor requested follow up). Days in ACT hospitals were defined as the calendar difference between dates of admission and final discharge, midnight to midnight.⁹ The mean of the number of days spent in hospital by those in the smoking group was nearly double that of those in the non smoking group. It is interesting that more vaccinations were performed for the smoking group.

Not every rubric studied produced a greater number of diagnoses for the children of smoking parents. For example there were 27 diagnoses of croup and 16 of these occurred in the non smoking group. Skin disease results were similar, 24 to 39, as were those of rubella and modified pertussis. No child in the survey died but a baby born to a family whose sibling was in the study died from Sudden Infant Death Syndrome. Both parents of this baby smoked.

Using chi square, all the data for the

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Disease/health problem	Parent(s) smoking	Parents non smoking
Winter consultations	172	138
Spring consultations	107	82
Summer consultations	48	45
Autumn consultations	71	39
Respiratory diagnoses	216	154
Nervous and sense	104	63
Infectious disease	68	34
Preventive	40	26
URTI, pharyngitis	125	95
Otitis media	80	49
Gastroenteritis	37	17
Total diagnoses	502	372
Total consultations	398	308

URTI: upper respiratory tract infection

24 categories were studied — there were 2,243 observations for the smoking group and 1,614 for the non smoking. Chi square equalled 36.34 with 24 degrees of freedom and the probability level (p) equals 0.0509, which is almost significant at the five per cent level. However, there were five cells with expected frequencies less than five (these were for both groups in rubella, the non smoking group in scarlet fever and both groups in modified pertussis). If these rows are omitted chi square equals 34.91 with 22 degrees of freedom and p equals 0.0396 which is significant at the five

per cent level. If the rows were combined then chi square equals 33 and p equals 0.0619 which is significant at the 10 per cent level.

The means of the diagnoses per patient over 18 months were calculated. Figure 1 shows a greater mean of consultations (7.6 to 5.9) and diagnoses (9.6 to 7.1) for the children of smoking parents. Breaking consultations and diagnoses into age groups showed a continuing dominance of the smoking group in all ages except for age two to three years. Figure 2 shows the breakdown of total consultations by season with smoking group

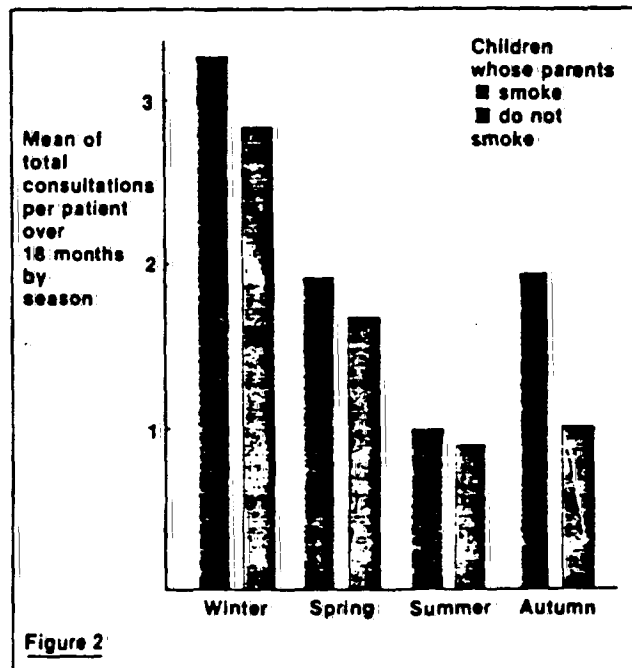
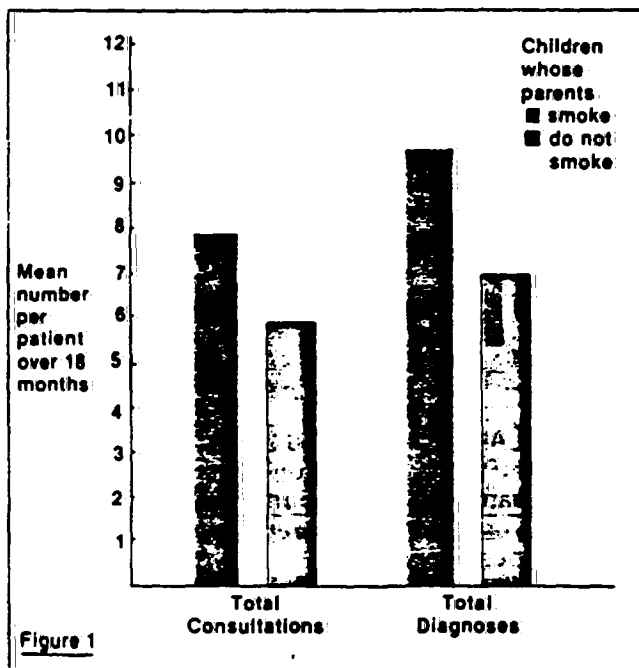
Disease/health problem	Parent(s) smoking	Parents non smoking
Days in ACT hospitals	80	41
Wheezing on auscultation (total)	45	32
Wheezing on auscultation (initial)	28	17
Vaccinations	39	20
Conjunctivitis	15	7
Trauma	13	9
Tonsillitis	9	6
Scarlet fever	8	2

ACT: Australian Capital Territory

dominance in all seasons but especially in autumn. Breaking down winter and spring consultations by age showed the smoking group again ahead in all ages, except for age two to three years. Figure 3 compares the means of

The smoking group children had more diagnoses of respiratory disease, nervous and sense organ disease, trauma and infectious disease.

diagnoses per patient for the larger classifications of illnesses. The smoking mean was higher for respiratory (4.1 to 3.0), nervous and sense organ, infectious, preventive and accident groupings but not for skin disease. For the ICHPPC — 2 rubrics (Figure 4), the



PASSIVE SMOKING

means were URTI, pharyngitis (2.4 to 1.8), otitis media (1.5 to 0.9), vaccinations (0.8 to 0.4) and gastroenteritis (0.7 to 0.3). In each of these categories the smoking group showed more diagnoses.

Discussion

Parental anxiety was a variable which was not included in the matching procedure. It may have played an important role as smokers exhibit more neurotic symptoms than non smokers¹⁸ and it may be this factor that drives the smoking parents to consult the doctor with their children. However, otitis media is an excellent tracer disease where one would expect parental anxiety to express itself equally in both groups.¹¹ There was a marked increase in attendance for otitis media in the smoking group. A more recent study by the author based on the same children, has shown a dose response relationship. This suggests an actual effect of sidestream smoke, possibly altering the IgE antibody on the eustachian tube mucosa, or the increase of upper respiratory infection.¹²

Respiratory disease diagnoses were seen more in the smoking group and include both upper and lower respiratory tract infections, pharyngitis, tonsillitis, scarlet fever and wheezing. These are similar findings to previous

studies on the effects of smoking. The greater number of tonsillitis diagnoses in the smoking group correlate with another study which has demonstrated a higher rate of tonsillectomy in the children of smokers.¹³

Wheezing was a clinical measure¹⁴ as airflow meters are difficult to use with young children. Other studies of older children have shown forced expiratory volume (FEV) changes directly related to the child's mother's smoking.^{15, 16} By a seasonal analysis, respiratory disease dominated the smoking group, with the smallest difference between the groups occurring in summer, when, one assumes, children are outdoors more often and away from sidestream smoke.

The tracer disease otitis media was expected to express itself equally in both groups but it featured more prominently in the smoking group.

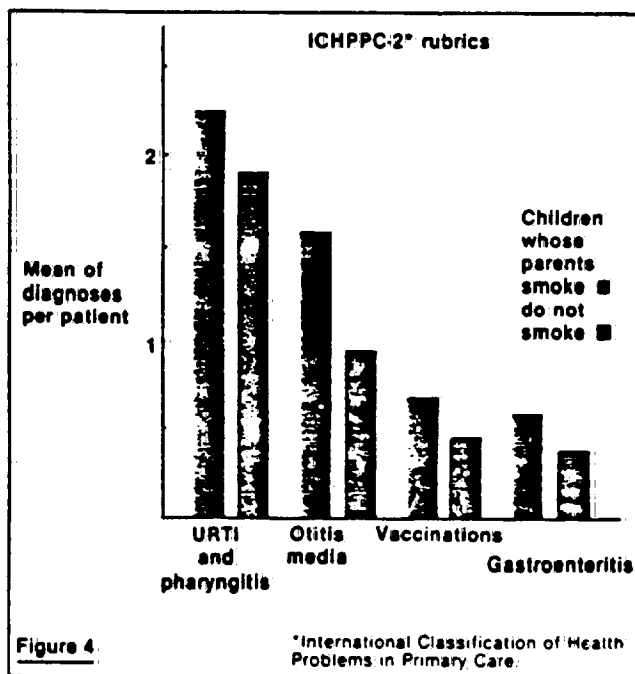
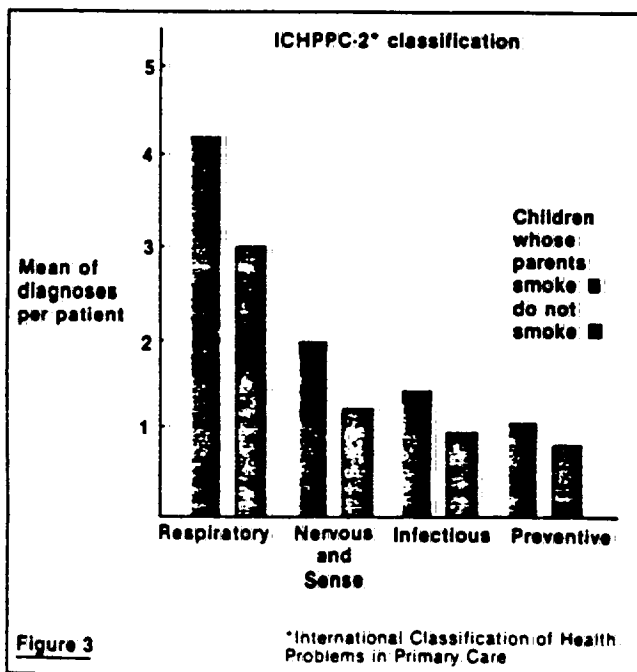
Gastroenteritis diagnoses were greater in the smoking group. Parental anxiety may be a factor here. Breast feeding has a protective effect and one asks, do breast feeders tend to be non smokers? Carbon monoxide poisoning can mimic gastroenteritis.¹⁷

Conjunctivitis diagnoses predominated in the smoking group. This find-

ing is supported by another study which showed sidestream smoke as a cause of measurable physical change to the tear film.¹⁸

The mechanism of disease production from cigarette sidestream smoke is unknown. This smoke has higher concentrations of potentially noxious substances than that inhaled by the smoker. These include carbon monoxide and the carcinogens 3,4-benzo (a) pyrene, ammonia and dimethylnitrosamine.^{19, 20} It increases venous carboxyhaemoglobin, serum nicotine and thiocyanate.^{21, 22} Cigarette smoke has 50 suspected carcinogens²³ and can affect mammalian tissue cultures.²⁴ It can trigger angina in the non smoking adult as well as significantly reducing forced expiratory flow by 25 to 75 per cent.²⁵

The sample in this study had a similar general morbidity pattern to another group of children studied in a Newcastle practice several years ago.²⁶ Future studies should include the child minder's smoking habits as another variable and use tracers such as cotinine to detect the presence of 'passive' smoke. The study is limited to this sample and extrapolation of the findings cannot be made universally but they definitely indicate that further studies should be made. The age group involved (young children) constitutes an important part of primary



ATIVAN[®] Prescribing Information

Composition Lorazepam

Actions — A benzodiazepine derivative remotely related to chlordiazepoxide and diazepam, and closely related to oxazepam. It has a therapeutic equivalence in doses about one-fifth that of diazepam and one-twentieth of that of oxazepam and chlordiazepoxide. In humans, lorazepam has an anxiolytic effect and relief of symptoms of both free floating and somatic anxiety has been demonstrated. An anticonvulsant effect has been confirmed but is yet to be delineated. An amnesic effect is seen at high dosage. No muscle relaxant property is seen in therapeutic dosage. Lorazepam has a sedative hypnotic effect at doses within the recommended therapeutic range, with low initial dosage and adjustment to individual response the anxiolytic effect may be separated from the sedative hypnotic. Lorazepam is metabolised in the liver and excreted mainly in the urine, almost entirely as the glucuronide. Peak plasma levels of free drug are obtained over one to six hours.

Indications — Emotionally induced autonomic symptoms such as headache, insomnia, gastrointestinal upsets, palpitation etc. Anxiety as a complicating factor in organic disease (Lorazepam may be a valuable adjunct because of its compatibility with other medications in the treatment of conditions such as cardiovascular disease and peptic ulcer). Symptomatic relief of anxiety and tension in psychoneurosis and anxiety reactions.

Note Lorazepam is not indicated in psychotic emotional reactions.

Contraindications — History of hypersensitivity to lorazepam or other benzodiazepines. Acute narrow angle glaucoma (Lorazepam may be used in open angle glaucoma which is being treated appropriately).

Use in children — Because of lack of sufficient clinical experience, use in children under 6 years of age is not recommended.

Precautions — Amnesia has been frequently reported after peroral use of benzodiazepines; in a few susceptible individuals amnesia has been reported after oral dosage of lorazepam (3 mg) or diazepam (20 mg).

Patients should be warned against operating dangerous machinery or driving motor vehicles. Care should be taken to warn patients that their tolerance to alcohol or other CNS depressants may be lowered.

When therapy is no longer needed lorazepam dosage should be decreased gradually. Withdrawal symptoms have been reported after abrupt discontinuation of benzodiazepines especially after an extended period of high dosing.

Special care is needed in renal or hepatic dysfunction.

Use in pregnancy — Safety in pregnancy has not been established. Use in lactation. In therapy of the breast feeding mother, lorazepam might be expected to appear in milk as do other benzodiazepines but no direct data are available.

Adverse Reactions — The commonest effects are CNS in origin and include sleepiness, drowsiness, dizziness, headache, nausea and vomiting. Other reactions are ataxia, depression, blurred vision, diplopia, dry mouth or hypersalivation, confusion, dysarthria, hypotension, incontinence, changes in libido, constipation, tremor, vertigo, skin rash.

Paradoxical reactions such as hyperexcitability, anxiety, hallucinations, increased muscle spasticity, insomnia, rage or sleep disturbances have been reported and are indications for the drug to be discontinued.

Benzodiazepines have been reported to cause isolated cases of neutropenia and/or jaundice, periodic blood counts and liver function tests are advisable during long-term therapy.

Interactions — Patients should be advised to abstain from alcohol and other CNS depressants. If the clinician desires to use combined therapy with other psychotropic or antidepressant drugs, consideration should be given to the pharmacology of the other agents, particularly with compounds known to potentiate its action such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants.

Overdosage — Treatment. Management of overdose is by general supportive measures along with gastric lavage. IV fluids should be given and an adequate airway maintained.

Dosage and Administration — In mild to moderate anxiety (as seen in general practice): 2 to 3 mg daily with a range up to 6 mg. The initial dose may be given at night to obviate drowsiness early in therapy. A twice daily regimen is often sufficient but some patients may need thrice daily dosage. The final dose is given preferably one hour before retiring. If insomnia is predominant, the bedtime dose may be twice that for the morning. Geriatric patients will probably respond to lower daily doses. In the severely disturbed patient (as seen in psychiatric practice): Doses of the order of 5 to 10 mg or more daily may be required.

For pre-surgical medication: 2 to 4 mg of Ativan the night before and/or 1 to 2 hours before the operation or procedure.

Children: Initiate therapy with the lowest dose (no more than 0.5 mg) and increase as required. Ativan is not recommended for children under six years.

Presentation — Tablets, 1 mg (off white, scored, marked 1 mg, Wyeth logo on reverse); 50's; 2.5 mg (yellow, scored, marked 2.5 mg, Wyeth logo on reverse); 50's.

Oral solution: 1 mg/5 mL (white, clear, effervescent, with lemon flavour). Presentation: 100 mL and 250 mL bottles; or 600 tablets, 2 packets of 300 tablets.

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PASSIVE SMOKING

care in this country.²⁷ Many people, especially women, smoke at the time they begin their families and this group particularly should be encouraged by their general practitioners to give up smoking.²⁸

Conclusion

There were differences between the smoking and non smoking groups in this sample and overall, they were great enough to be almost significant at the five per cent level. Upper and lower respiratory disease, conjunctivitis, otitis media, infectious disease and accidents featured more strongly in the smoking group. One would expect the tracer disease — otitis media — to express itself equally in both groups but in fact it featured more prominently in the smoking group. The smoking group consulted more and spent more days in hospital. Larger studies in a primary care setting are strongly recommended.

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Pukander, J., Luotonen, J., Timonen, M. "Risk Factors Affecting the Occurrence of Acute Otitis Media among 2-3-Year-Old Urban Children" Acta Otolaryngol 100: 260-265, 1985.

ABSTRACT. The factors affecting the occurrence and recurrence of acute otitis media (AOM) were studied among 471 2-3-year-old children in two cities in Finland. Of these children, 188 had experienced ≥ 3 attacks of AOM, 76 had had 1-2 attacks and 207 no otitis attacks (=control group). The study showed that the risk of recurrent AOM was increased among those children attending day-care nurseries as well as among those who had several siblings. Proneness to rhinorrhea and exposure to passive smoking at home was associated with an increased risk of AOM, while prolonged breast-feeding (> 6 months) seemed to reduce it. No correlation was found between the risk of recurrent AOM and the place of residence or type of housing, the parental otitis history, or atopic diathesis of a child. Thus the study suggested that to protect a young child from AOM we should promote breast-feeding and home-care for babies as well as avoid smoking in the home.

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Risk Factors Affecting the Occurrence of Acute Otitis Media among 2-3-Year-Old Urban Children

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Pukander J, Luotonen J, Timonen M, Karma P. Risk factors affecting the occurrence of acute otitis media among 2-3-year-old urban children. *Acta Otolaryngol (Stockh)* 1985; 100: 260-265.

The factors affecting the occurrence and recurrence of acute otitis media (AOM) were studied among 471 2-3-year-old children in two cities in Finland. Of these children, 188 had experienced ≥ 3 attacks of AOM, 76 had had 1-2 attacks and 207 no otitis attacks (= control group). The study showed that the risk of recurrent AOM was increased among those children attending day-care nurseries as well as among those who had several siblings. Proneness to rhinorrhea and exposure to passive smoking at home was associated with an increased risk of AOM, while prolonged breast-feeding (>6 months) seemed to reduce it. No correlation was found between the risk of recurrent AOM and the place of residence or type of housing, the parental otitis history, or atopic diathesis of a child. Thus the study suggested that to protect a young child from AOM we should promote breast-feeding and home-care for babies as well as avoid smoking in the home. *Key words:* middle ear, epidemiology, environmental factors.

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Acute otitis media (AOM) is a very common affection among young children. Typical of the disease is a high incidence of recurrences, especially during the first few years of life (1, 2, 3). One reason for this is that the immunological defence mechanisms of a child mature relatively slowly during the first years of life (4) leaving a young child prone to infections. But environmental factors such as population density (5) and air pollution (6) have also been shown to affect the occurrence of AOM considerably.

The purpose of this study was to evaluate factors predisposing to recurrent AOM in a population of 2-3-year-old urban children in Finland.

MATERIAL AND METHODS

The patient material of the present study consisted of 264 consecutive 2-3-year-old children who visited, because of AOM (characterized by acute symptoms and effusion in the middle ear) the Out-Patient Department of Otolaryngology or Pediatrics of the University Central Hospitals of the cities of Tampere and Oulu in Finland. There were 120 girls and 144 boys. As a non-otitis control-group we took 207 children (106 girls, 101 boys) of the same age from the municipal children's health centres of the same two cities. The enrolment criterion was freedom from AOM thus far in life. The mean age of the otitis patients was 2.90 years and that of non-otitis controls, 3.09 years.

During the Out-Patient AOM visit, information regarding the number of attacks of AOM experienced thus far during the child's lifetime as well as epidemiologic data of interest for the study was obtained by means of a questionnaire to the parents of the otitic children. A

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similar questionnaire was filled in by parents of non-otitic children in the children's health centres. The questionnaire comprised the following questions: The duration of breast-feeding, the day-care arrangements, the number of siblings and their otitis history, presence of allergic manifestations, occurrence of rhinorrhea and other respiratory infections, the otitis history and smoking habits of the parents and the family's place of residence.

To study the factors associated with AOM, the children were classified into three groups according to the otitis history (the questionnaire-visit included): no attacks (= control group, $n=207$) 1 or 2 attack(s) ($n=76$) and three or more attacks ($n=188$). For statistical analysis we used the χ^2 -test.

RESULTS

Of all children, 91 had been cared for in day-care centres for more than a 6-month period (Table I). They were found to have had AOM significantly more often than children cared for at home, whereas day-care within the family did not increase the number of otitis attacks. Also, on the other hand, the number of siblings in a child's family affected the frequency of AOM almost significantly, so that greatest risk of repeated attacks was found among those children who were from families with three or more children (Table II).

In the present study neither the place of residence (within the city limits) nor the type of housing affected the risk of contracting AOM. Likewise, no correlation was found between the parental otitis history and the occurrence of AOM in the children.

Breast-feeding—and especially its prolongation for over 6 months—seemed to protect a baby against AOM, and a significant negative correlation was found between the duration of breast-feeding and the number of otitis attacks (Table III).

In 202 families the parent(s) smoked and this was found significantly to sensitize a child to AOM compared with children from non-smoking families (Table IV).

Furthermore, a highly significant correlation was found between the occurrence of rhinorrhea (as compared with its frequency in other children in the neighbourhood) and a liability to repeated otitis attacks (Table V).

Table I. Day-care arrangements and occurrence of AOM

Day-care form ^a				
Number of attacks	Day-care ^b centre	Family ^b day-care (home)	Own home	
0	28	41	133	
1-2	16	15	45	
≥3	47	35	102	
Total	91	91	280	
Significance of partitioned columns				
		χ^2	DF	<i>p</i>
Day-care centre vs. own home		8.486	2	0.014
Day-care centre vs. family care		4.237	2	0.120
Family care vs. own home		0.171	2	0.918

^a Data not available from 9 children.

^b Cared for ≥6 months outside own home.

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16.6% of all the children showed some atopic manifestation; infantile eczema was found in 11.8%, asthma in 2.3% and hay-fever in 2.5%. No significant correlation was found between the allergic diathesis and the occurrence of AOM.

DISCUSSION

Because of the commonness of AOM (7) and the magnitude of human suffering and economic loss it causes, every effort must be made to reduce its frequency. Therefore epidemiological studies of the factors affecting the occurrence of (recurrent) AOM and the possible removal of these factors are of importance.

In the majority of cases, AOM is nowadays preceded by an upper respiratory viral infection (8, 9, 10, 11). One of the most outstanding manifestations of respiratory infection is rhinorrhea. In the present study, a close correlation was found between a proneness to rhinorrhea and the recurrence of otitis attacks. Although we did not distinguish between allergic and viral rhinorrhea, the finding might suggest that the mucosa of one part of the respiratory tract—the middle ear—reflects the changes of another part—the nose—regardless of the background of the damage.

Viruses tend to spread more easily, the higher the population density in a certain area. Thus the number of human contacts in a child's daily life plays a very important part in the

Table II. *Size of the family and occurrence of AOM*

Number of attacks	Number of siblings		
	0	1	≥2
0	97	80	30
1-2	30	35	11
≥3	64	77	47
Total	191	192	88
Significance of partitioned columns			
0 vs. ≥2		χ^2 11.449	DF 4 P 0.022

Table III. *Breast-feeding and occurrence of AOM*

Number of attacks	Duration of breast-feeding (months)			
	<1	1-3	4-6	>6
0	16	89	43	59
1-2	11	32	15	18
≥3	36	73	41	38
Total	63	194	99	115
Significance of partitioned columns				
<1 vs. 1-3		χ^2 9.178	DF 2	P 0.010
<1 vs. 4-6		5.571	2	0.062
<1 vs. >6		12.252	2	0.002

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likelihood of contracting AOM. Day-care centres with many children in the same place create favourable conditions for respiratory epidemics (12), with AOM as a sequel. This is confirmed in our study by the children who attended day-care centres and who contracted AOM more frequently than children cared for in their own homes, a finding also consistent with some earlier reports (13, 14, 15, 16). The greater size of the family increases the number of daily human contacts of a child and may work analogously with the day-care. Accordingly, in the present study, the children from families with three or more children contracted AOM more frequently than children from smaller families. Cunningham (17) also stated that the presence of other children was associated with increased morbidity in respiratory infections, otitis media included. On the other hand, Watkins et al. (18) and Vinther et al. (19) did not find any correlation between the number of siblings and the frequency of AOM, and in the series of Paterson & MacLean (20) the non-otitis control children even belonged to larger families compared with children with AOM. Consequently, although the reports on the effect of family size on the liability of a child to contract AOM are not all in agreement, we strongly recommend that children should be cared for in small, separate, family-size groups (12) instead of large day-care centres.

Prolonged breast-feeding has been found to protect a baby against respiratory infections in general (18, 21). This is thought to be due to the transmission of specific human immunoglobulins in breast milk thus improving the immunological defence mechanisms of an infant (22, 23, 24). Furthermore, the immunoglobulins may also coat the bowel mucosa, thus preventing the absorption of harmful cow's milk proteins (25). In the present study,

Table IV. *Exposure to passive smoking and occurrence of AOM*

Number of attacks	Smoking of parents(s)	
	No	Yes
0	136	71
1-2	40	36
≥3	93	95
Total	269	202

Table V. *Rhinorrhea and occurrence of AOM*

Number of attacks	Occurrence of rhinorrhea compared with other children in neighbourhood*				
	Never	Less than in other children	Equally with other children	More than in other children	Continuously
0	18	75	112	2	0
1-2	3	13	53	6	0
≥3	0	9	128	37	10
Total	21	97	293	45	10
Significance of the whole contingency table			χ^2 119.99	DF 8	P <0.001

* Data not available from 5 children.

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children who had been breast-fed for over 6 months experienced significantly fewer episodes compared with those breast-fed for less than 1 month. This is in accordance with reports indicating a lower recurrence rate of AOM among infants breast-fed over a relatively long period, i.e. 6–12 months (25, 26), and with the finding that infants breast-fed for less than 3 months experienced their first AOM significantly earlier than those breast-fed for longer periods (27). On the other hand, no significant correlation between the duration of breast-feeding and the liability to contract AOM was found by Kjellman (28) and Vinther et al. (19), probably because of the design of these studies. However, evidence strongly supports the advisability of breast-feeding, which in fact is becoming more fashionable again after a period of underrating this natural way of nourishment (18, 29, 30). This favourable development should be encouraged.

Parenteral smoking exposes the whole family to smoke and this "passive smoking" has been found to predispose children to respiratory infections (6, 31, 32, 33). Accordingly smoke must be a predisposing factor to AOM, too. However, as far as we know there are no earlier reports indicating an increased risk of AOM among children from smoking families. On the contrary, Vinther et al. (19) did not find any such connection, probably because of the masking effect of other parameters (e.g. day-care) in their study. The problem of passive smoking has become more important along with changes in housing, with increasingly more families living in cities in rather small flats, where the amount of indoor smoke reaches much higher concentrations, compared with old-fashioned farm-houses.

Opinions of the role of allergy in the etiology of AOM are not unanimous. In the present study no constant correlation was found between atopic diathesis of a child and the frequency of AOM, an observation also made by Kjellman (28). Many studies, however, have shown an association between atopic allergy and a tendency to recurrent or prolonged otitis, i.e. secretory otitis media (25, 34, 35), especially among children who also had a positive family history of allergy (36). On the whole, the role of allergy *per se* as a risk factor to AOM might not be too straightforward after all, and further studies are warranted to clarify this.

In conclusion, our study revealed that certain factors associated with the proness of small children to acute and recurrent otitis media can be regarded as a consequence of social and cultural changes. When trying to reduce the frequency of AOM in children, these factors must be taken into account. These include the favouring of breast-feeding, the promotion of home-care for small children, and the avoidance of smoking at home.

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ABSTRACT: Risk factors for acute upper respiratory tract disease in childhood were evaluated in a population-based sample of the Atlanta metropolitan area. Mothers from 449 households containing 575 children less than 5 years of age were selected by random-digit dialing and questioned about upper respiratory tract infection and ear infection occurring in their children during the preceding 2 weeks. Household demographic and socioeconomic characteristics, maternal smoking history and child day-care attendance and breast-feeding information were also obtained. For children less than 5 years of age, the reported incidence of upper respiratory tract infection was 24%, and of ear infection, 6%. Controlling for the other variables measured, day-care attendance was associated with a significantly increased risk of both illnesses. For upper respiratory tract infection, increased risk was present for all children attending daycare ($P = .02$, odds ratio = 1.6), whereas for ear infection, risk could be demonstrated only for full-time attendees ($P = .005$, odds ratio = 3.8). Maternal smoking was a second independent risk factor for a child's having upper respiratory tract infection (odds ratio = 1.7, $P = .01$). Thirty-one percent of all upper respiratory tract infection among day-care attendees and 66% of all ear infections among full-time day-care attendees were attributable to day-care attendance. Given the proportion of children in day-care, 9% to 14% of the total burden of upper respiratory tract disease in this population was daycare related. As use of child day-care facilities has increased, this specific exposure has become a major factor contributing to transmission of acute upper respiratory tract disease in childhood.

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Childhood Upper Respiratory Tract Infections: To What Degree Is Incidence Affected by Day-Care Attendance?

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ABSTRACT. Risk factors for acute upper respiratory tract disease in childhood were evaluated in a population-based sample of the Atlanta metropolitan area. Mothers from 449 households containing 575 children less than 5 years of age were selected by random-digit dialing and questioned about upper respiratory tract infection and ear infection occurring in their children during the preceding 2 weeks. Household demographic and socioeconomic characteristics, maternal smoking history and child day-care attendance and breast-feeding information were also obtained. For children less than 5 years of age, the reported incidence of upper respiratory tract infection was 24%, and of ear infection, 6%. Controlling for the other variables measured, day-care attendance was associated with a significantly increased risk of both illnesses. For upper respiratory tract infection, increased risk was present for all children attending day care ($P = .02$, odds ratio = 1.6), whereas for ear infection, risk could be demonstrated only for full-time attendees ($P = .005$, odds ratio = 3.8). Maternal smoking was a second independent risk factor for a child's having upper respiratory tract infection (odds ratio = 1.7, $P = .01$). Thirty-one percent of all upper respiratory tract infection among day-care attendees and 66% of all ear infections among full-time day-care attendees were attributable to day-care attendance. Given the proportion of children in day care, 9% to 14% of the total burden of upper respiratory tract disease in this population was day care related. As use of child day-care facilities has increased, this specific exposure has become a major factor contributing to transmission of acute upper respiratory tract disease in childhood. *Pediatrics* 1987;79:55-60; upper respiratory tract infection, day-care attendance.

Infections of the upper respiratory system are the most common illnesses affecting children less than 5 years of age in the developed world. Although

these illnesses, including acute upper respiratory tract infection and otitis media, may occasionally progress to more severe disease, most often they are self-limited. Despite their relatively benign nature, however, upper respiratory tract infectious illnesses are important causes of childhood morbidity, and their treatment consumes a substantial portion of available health care resources.¹

During the past decade, it has been demonstrated that risk of a number of childhood infections, including hepatitis,² diarrheal diseases,³ and invasive *Haemophilus influenzae*,⁴ is increased by day-care attendance. During this same time, the number of children younger than 5 years of age in the United States who are enrolled in day care has undergone a dramatic increase.⁵ Although several studies have suggested that the risk of upper respiratory tract disease may be increased for some day-care attendees,⁶⁻⁸ the importance of this association has not been well defined.

In this study, we examined risk factors for acquisition of infections of the upper respiratory system in children less than 5 years of age and specifically evaluated the role played by day-care attendance. Using population-based data, we determined the amount of illness attributable to this increasingly common childhood exposure.

METHODS

A cross section of all households containing children less than 5 years of age in Atlanta was surveyed by telephone from mid-July through mid-September 1984.

Sampling Procedure

Telephone numbers consisting of prefixes serving the study area and four randomly selected final

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digits were generated by computer. Every possible telephone number in the seven counties composing the metropolitan area (population 1.9 million) had an equal likelihood of being selected and called; no call-clustering techniques were used. Each number selected was called at least twice during business hours and at least six times during evenings and weekends before being discarded. Only households with children less than 5 years of age were enrolled.

Questionnaire Administration

Using a standardized questionnaire, trained interviewers obtained informed consent and then collected information from the guardian of the children in the household, preferably the mother. Data obtained included household demographic and socioeconomic characteristics, current maternal smoking history, and current breast-feeding and day-care attendance information for all children less than 5 years of age. All children within a given household were enrolled to ensure that our sample accurately represented all children in the study area with respect to household size and other related characteristics. A 15% sample of completed questionnaires was validated with a follow-up telephone call; no child's illness or day-care status was reclassified as a result of these calls.

Definitions

History of recent acute respiratory infection (cough, cold, or ear infection) was obtained directly from the child's guardian.^{6,7,9} Because independent physician confirmation of illness was not required, we have used the term "ear infection" rather than otitis media to denote parental reported cases of infections of the ear. Criteria including antibiotic administration and physician visit were used if respondents needed clarification. We did not attempt to identify specific etiologic agents. Incidence of disease rather than duration of symptoms was assessed. To limit interviewer and respondent bias, illness history was elicited before parents were asked about day-care attendance. Children were considered case children if they had been ill with upper respiratory tract infection or ear infection at any time during the 2 weeks before the interview was conducted. Day care was defined as regular (>4 h/wk) supervised care of at least two unrelated children. Each child's day-care status was determined individually, based on enrollment at the time of interview. Part-time enrollment was defined as five to 39 hours' attendance per week and full-time as 40 or more hours per week.

Analysis

Two analyses of risk factors were undertaken,

one for children reported to have upper respiratory tract infection and the other for children reported to have ear infection. An automatic interaction detection program was used to assist in selection of variables for inclusion in an unconditional logistic regression model. Only associations that were biologically plausible were considered. We did not attempt to analyze or control for transmission of illness within households because we could not distinguish between primary and secondary cases. The number of children younger than 5 years in the household, a variable included in the model, may serve as a surrogate for intrafamilial spread. Final models were obtained by first putting all candidate variables into the model and then eliminating any variable that was not significant and whose elimination did not alter the odds ratio estimates of significant variables by more than 15%. Etiologic fractions among exposed groups (EF_e) were calculated by the formula: $EF_e = (\text{probability of disease in exposed} - \text{probability of disease in unexposed}) / (\text{probability of disease in exposed})$ and were standardized for the entire population by weighting the values from individual strata according to the percentage of the population represented by that strata. The disease probabilities used were those determined by the regression model.

RESULTS

A total of 3,952 households in the study area were surveyed. Of these, 3,387 contained no children younger than 5 years, 78 were unwilling to answer whether children were present and 487 contained at least one young child. Of these latter households, complete interviews were obtained for 449 (92%). Twenty-six percent of households (118) contained more than one child, and information regarding illness was collected for 575 children.

Upper Respiratory Tract Infection

Twenty-four percent of the children surveyed (139/575) were reported to have had an upper respiratory tract infection during the 2 weeks before the interview. The incidence of reported illness was divided equally by sex with 24% of both boys (75/307) and girls (64/268) affected. Race did not appear to be a significant risk factor; illness was reported for 23% of white children (96/421), 27% of black children (40/146), and 40% of children of other races (4/10). The frequency of upper respiratory tract infection did vary somewhat with age; incidence in children younger than 36 months was 27% (91/338), and in children 36 months or older, 20% (47/232).

On univariate analysis, children who attended

day-care facilities appeared to be more likely than children who did not attend to have had symptoms of an upper respiratory tract infection during the 2 weeks preceding the interview (32% [55/175] of attendees *v* 21% [84/400] of nonattendees; $P = .01$, χ^2). A significant difference in risk between part-time and full-time attendance could not be demonstrated, although there was a suggestive trend in children younger than 36 months (42% [23/55] incidence in full-time attendees *v* 28% [11/39] in part-time attendees, $P = .2$, Fisher exact test). The type of day-care facility, ie, residential *v* nonresidential, and the length of time the child had been attending were not statistically associated with the likelihood of upper respiratory tract infection.

The association of day-care attendance with upper respiratory tract infection was further evaluated by logistic regression in a model that contained other variables considered to be possible risk factors for disease. These variables included family income, crowding (dichotomized at less than *v* equal to or more than one person per room), and number of children less than 5 years of age, maternal smoking, and child's race and age (dichotomized at 36 months). Current breast-feeding was included as a possible protective factor in children less than 6 months of age.

In this model, children who attended day care were significantly more likely than children who did not attend to have had a parent-reported upper respiratory tract infection during the 2 weeks before interview (odds ratio = 1.6, $P = .02$, Fig 1). In addition to day-care attendance, a second factor, maternal smoking, was also associated with increased risk of upper respiratory tract infection (odds ratio = 1.7, $P = .01$). The effects of day-care attendance and maternal smoking were independent of one another. Child's age, although itself not

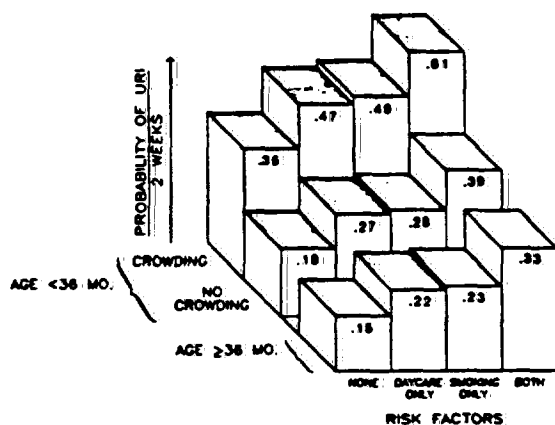


Fig 1. Probability of upper respiratory tract infection according to age, crowding, maternal smoking, and day-care status.

a risk factor (odds ratio = 1.2, $P = .4$), did significantly modify the effect of a third variable, household crowding. Living in crowded conditions was significantly associated with upper respiratory tract infection in children younger than 36 months (odds ratio = 2.4, $P = .02$) but not in children 36 months or older (odds ratio = 0.6, $P = .4$). No statistically significant association with risk of upper respiratory tract infection was seen for family income, number of children less than 5 years, and child's race, and no protective benefit of breast-feeding could be demonstrated (Table 1).

Clustering of illnesses within households did not seem to significantly affect the association of upper respiratory tract infection with day-care attendance. This relationship in households with only one child less than 5 years of age was similar to that in households with two ill children (odds ratio = 1.73 *v* 1.72), and the prevalence of day-care attendance in ill children from households containing no other children less than 5 years was similar to that observed in children from households with another ill sibling (41% [35/85] *v* 40% [12/30]).

Ear Infection

Six percent (34/575) of children less than 5 years of age were reported to have had an ear infection during the 2 weeks before the interview. Ear infection was reported more often for boys than girls (7.2% *v* 4.5%), but this difference was not statistically significant. Black children and white children were affected equally (6.1%); none of the ten children of other races were reported ill. Compared with upper respiratory tract infection, the incidence of ear infection was more influenced by age. Incidence was 8.6% (29/337) in children 0 to 35 months of age and 2.1% (5/233) in children 3 or 4 years of age. Children with ear infection were significantly more likely than children without ear infection to have had upper respiratory tract infection symptoms during the preceding 2 weeks (65% [22/34] *v* 22% [116/535]; odds ratio = 6, $P < .001$, Fisher exact test).

Univariate analysis suggested that, as with upper respiratory tract infection, children attending day

TABLE 1. Variables Not Included in Final Upper Respiratory Tract Infection Model

Variable	Odds Ratio (Point Estimate)	P Value
No. of children <5 yr	0.7	.17
Race	1.1	.76
Breast-feeding	1.0	.98
Income (\$)		
0-19,999	1.0	
10-34,999	1.5	.14
≥35,000	1.0	.91

care were at increased risk for development of ear infection. For ear infection, however, only children who attended a day-care facility 40 or more hours per week could be shown to be at increased risk. This association with full-time attendance was present when either all children or only children younger than 36 months were evaluated (Table 2). Although the number of children with ear infection who attended day-care full time was relatively small, the type of day-care facility, ie, residential v nonresidential, and the length of time the child had been attending did not appear to be associated with increased risk of disease.

The association between full-time day-care attendance and ear infection was evaluated in a logistic regression model containing the same variables that were used for the upper respiratory tract infection analysis. Concomitant upper respiratory tract infection was not considered as a separate risk factor because this illness may, in many instances, represent an intermediate step between exposure to a risk factor and ear infection.^{8,10} Clustering of ear infections within a household occurred only once and, thus, was not a factor in analysis. In the ear infection model, full-time day-care attendance was strongly associated with increased risk of ear infection (odds ratio = 3.2, $P = .005$). Age was a second important predictor of disease, with children younger than 36 months at higher risk than children 36 months of age or older (odds ratio = 3.3, $P = .02$). Among young children, as with upper respiratory tract infection, crowding was an important factor predicting disease (odds ratio = 3.4, $P = .01$); in the older age group, data were insufficient to assess the effect of this variable (Fig 2). For ear infection, family income, number of children less than 5 years of age, maternal smoking, and child's race and breast-feeding status were not significantly associated with risk (Table 3). Two factors, maternal smoking and part-time day-care attendance, which were associated with the risk of upper respiratory tract infection, were not associated with the risk of ear infection. This finding may be due to the smaller numbers of children with ear infections and consequent lack of statistical power or

TABLE 2. Incidence of Ear Infection by Day-Care Attendance Status for All Children and Children 0 to 35 Months of Age

Day-Care Attendance Status	Incidence of Ear Infection (%)	
	All Children	0-35 Mo
Nonattendees	4.8 (19/395)	7.0 (17/244)
Part-time attendees	4.1 (3/73)	5.3 (2/38)
Full-time attendees	11.7 (12/102)	18.2 (10/55)
Status not available	(0/5)	(0/1)
Total	5.9 (34/575)	8.7 (29/338)

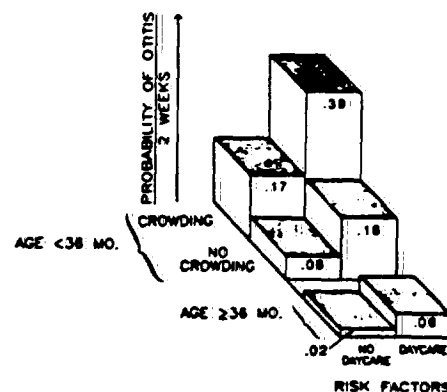


Fig 2. Probability of ear infection according to age, crowding, and day-care status.

TABLE 3. Variables Not Included in Final Ear Infection Model

Variable	Odds Ratio (Point Estimate)	P Value
No. of children <5 yr	0.7	.43
Maternal smoking	1.1	.82
Race	1.0	.93
Breast-feeding	1.9	.32
Income (\$)		
0-19,999	1.0	
20-34,999	0.9	.87
≥35,000	0.8	.73

alternatively to actual differences in risk factors for these two syndromes.

Attributable Risk

Perhaps the most meaningful measure of the amount of upper respiratory tract disease associated with day-care attendance is the etiologic fraction among the exposed children or $EFe_{(day-care)}$, which can be interpreted as the proportion of respiratory illness among children who attend day care that is directly related ("attributable") to this exposure.

In this study, the $EFe_{(day-care)}$ for upper respiratory tract infection, adjusted for the other variables shown to be associated with upper respiratory tract infection, was 31%. Thus, approximately one third of upper respiratory tract infections in children who attend day care may be attributable to this specific exposure. The $EFe_{(day-care)}$ for upper respiratory tract infections varied slightly by age and was 30% for children younger than 36 months and 33% for children 36 months of age or older.

For ear infections, the $EFe_{(full-time day-care)}$ was 66%, standardized for the other variables shown to be associated with ear infection, and thus approximately two thirds of ear infection contracted by full-time day-care attendees may be directly re-

TABLE 4. Etiologic Fraction Among Exposed Groups ($EFe_{day-care}$) and Population Attributable Risk of Upper Respiratory Tract Infection and Ear Infection Associated with Day-Care Attendance

Child's Infection and Age (Mo)	$EFe_{day-care}$	Children Attending Day-Care (%)	Population Attributable Risk (%)
Upper respiratory tract			
0-35	.30	29	9
≥36	.33	34	11
Ear infection			
0-35	.64	16	10
≥36	.68	20	14

lated to that specific exposure. The age-specific $EFe_{full-time\ day-care}$ for ear infection was 64% for children 0 to 35 months of age, those at highest risk, and 68% for children 3 and 4 years of age.

The amount of upper respiratory tract disease in all young children that is directly related to day-care attendance (the etiologic fraction among the population, also called the population attributable risk) depends not only on the proportion of illness related to attendance but also on the proportion of children who attend. This latter figure is likely to depend on a variety of factors including geographic region, season of the year, and age of the children involved. In Atlanta, during the summer of 1984, the population attributable risk for day-care attendance varied between 9% and 11% for upper respiratory tract infection and between 10% and 14% for ear infection, depending on child's age (Table 4).

DISCUSSION

Although more than 11 million children in the United States attend some form of day care,¹¹ estimates of risk have not been available for many of the illnesses to which these children are exposed, and the need for population-based studies has become increasingly apparent.^{11,12} In particular, although the association between day-care attendance and infections of the upper respiratory system was suggested more than 35 years ago,¹³ the contribution of day-care exposure to overall risk for these diseases has not been defined.

This study was designed to quantify the relation between day-care attendance and risk of childhood upper respiratory tract infections. Controlling for the effect of other risk factors, children in this cohort who were enrolled in day care were substantially more likely to have both upper respiratory tract infection and ear infection. Because these children were randomly selected from the general population, we could calculate that approximately

one third of upper respiratory tract infections among day-care attendees and two thirds of ear infections among full-time day-care attendees were directly related to attendance. Because data regarding the proportion of children in the population attending day-care facilities were also available, we were able to estimate that 9% to 14% of all upper respiratory tract infections and ear infections in children less than 5 years of age may occur as a result of day-care attendance, a figure generalizable to other areas to the extent that day-care attendance patterns in Atlanta are similar to attendance patterns elsewhere. These estimates provide a useful assessment of the influence of day-care attendance on the overall risk of upper respiratory tract infection in young children. Respiratory illness results in an estimated 17.4 million physician visits a year in the United States¹ and for otitis media alone, an estimated annual expenditure of more than \$2 billion.¹⁴

These percentages should be interpreted with appropriate caution. Having a child in day care may alter the likelihood that parents will notice and report illness in their children. This study determined a point estimate of risk based on parental reporting of illness during a 2-week period and, as such, should be viewed as only a first step in quantifying the effect of day-care attendance on the incidence of childhood upper respiratory tract infections. Nevertheless, the case definition based on parental reporting can be partially validated by the results of the analysis. If parents were reporting respiratory infections when no illness had occurred, one would not expect to find significant associations with crowding or maternal smoking. The substantial portion of upper respiratory tract infection linked to day-care attendance in this study suggests that it would be useful to determine whether specific etiologic agents may be particularly associated with this risk.

Additional studies that assess risk over season should be undertaken. For example, the risk of upper respiratory tract infection associated with day-care attendance calculated by this study may be a minimum estimate; day-care attendance may be more strongly linked with disease during the winter respiratory illness season when the likelihood of the introduction of upper respiratory tract infection into a day-care facility may be greater. Alternatively, a greater background incidence of viral infection during the winter might reduce the added risk associated with day-care attendance.

Several aspects of analysis other than the relation between upper respiratory tract illness and day-care attendance deserve comment. The similarity of the risk factor models for upper respiratory tract

infection and ear infection demonstrates the close association between these two illnesses and reaffirms the likely role of upper respiratory tract infections in the pathogenesis of ear infection.^{8,10} The data regarding maternal smoking underscore the link between passive exposure to smoke and development of upper respiratory tract infection in children.^{16,18} In this study, the proportion of upper respiratory tract infections in children of smoking mothers attributable to this exposure (34%) and the total population attributable risk (10%) were comparable to those calculated for day-care attendance.

As risk factors, however, there is a major difference between maternal smoking and day-care attendance. Whereas maternal smoking is totally preventable, day-care attendance is not. This difference highlights an increasingly obvious dilemma: child day care provides an irreplaceable service; yet, by its nature, it also results in enhanced transmission of infectious illnesses. The most practical approach to this problem—reduction of risk among those children who attend—rests on the assumption that differences in day-care facilities and children's exposures within those facilities may affect degree of risk. For diarrheal disease, this assumption seems warranted; risk has been shown to be influenced by a variety of specific day-care characteristics.³ Whether the same is true for respiratory disease remains an open question. Identification of specific factors that are associated with increased risk of upper respiratory tract disease within day-care facilities should be a primary goal of future study.

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Kallail, K.J., Rainbolt, H.R., Bruntzel, M.D. "Passive Smoking And Middle Ear Problems In Kansas Public School Children" J Commun Disord 20: 187-196, 1987.

This study was conducted by investigators who were interested in determining whether parental smoking influenced the incidence of middle ear problems in children. Children in the Kansas school system identified as having middle ear problems were compared with children who passed their school's hearing test. The researchers report that the investigation revealed that there were no differences between the two groups of children for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. Therefore, they concluded that "exposure to cigarette smoke in the home apparently was not a risk factor for middle ear problems in children.

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PASSIVE SMOKING AND MIDDLE EAR PROBLEMS IN KANSAS PUBLIC SCHOOL CHILDREN

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Survey data from parents of Kansas school children identified as having middle ear problems were compared to data obtained from parents of children who passed their school's hearing screening tests. The results of the investigation revealed that there were no differences between the two groups of children for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. Exposure to cigarette smoke in the home apparently was not a risk factor for middle ear problems in children.

INTRODUCTION

Research over the past half-century indicated that smoking causes cancer of the lung, larynx, oral cavity, and esophagus, and is significantly associated with pancreas, urinary bladder, and kidney cancer in both men and women (U.S. Department of Health and Human Services (DHHS), 1981). Further, a clear dose-response relationship has been established between smoking and a number of disease states.

Public awareness of the dangers of smoking has steadily increased over the years, including the danger of "passive" or involuntary smoking (DHHS, 1981). Several investigators have reported the negative effect of parental smoking on children's health (Bergman and Wiesner, 1976; Cameron et al., 1969; Cameron and Robertson, 1973; Colley, 1974; Colley et al., 1974; Comstock et al., 1971; Harlap and Davies, 1974; Kraemer et al., 1983; Saxton, 1978; Tager et al., 1979). One of the most frequently mentioned group of illnesses in children that has been associated with parental smoking was respiratory illnesses.

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The relationship of smoking and hearing abilities also has been investigated. Zelman (1973) found that smokers manifested greater hearing losses than nonsmokers, especially at the higher frequencies. Smokers also have been shown to have less temporary threshold shifts than nonsmokers (Dengerink et al., 1984). Cantrell (1970) reported that tobacco smoking caused eustachian tube malfunction and adversely affected the tympanic membrane. Marston, Sterrett, and McLennan (1980), however, found no significant effect on the admittance characteristics at the plane of the tympanic membrane in young adult smokers.

With regard to passive smoking and hearing ability in children, Saxton (1978) reported that infants whose mothers smoked during pregnancy manifested reduced or impaired auditory function as compared to infants whose mothers did not smoke. In addition, Kraemer and colleagues (1983) found that exposure to two or more household cigarette smokers increased children's risk for persistent middle ear effusions (PMEE) nearly threefold, fourfold with exposure to smoke from more than three packs per day. Children with the combined factors of atopy, nasal congestion, and exposure to cigarette smoke were six times more likely to manifest PMEE.

Examination of the literature indicated a paucity of data regarding the effects of passive smoking on the incidence of middle ear problems in children. In a reanalysis of some of the Kraemer et al. data, Rogers and colleagues (1984) suggested that there was not enough evidence to establish cigarette smoke exposure as a risk factor for PMEE. Further data, therefore, need to be obtained to determine the effects of passive cigarette smoking in children and middle ear problems. Also, because the Kraemer et al. data were obtained in Seattle, a city that has reduced air quality, similar information from a relatively "clean" air environment, such as Kansas (National Commission of Air Quality, 1981), should provide useful, additional data.

The purpose of the present investigation was to obtain survey data from parents of Kansas school children identified as having middle ear problems and compare them to data obtained from parents of children who passed their school's hearing screening tests. Information was obtained regarding the number of household smokers, the amount and type of household smoking, and the number of middle ear problems.

PROCEDURES

A questionnaire (see Appendix A) was developed to obtain the pertinent data from parents of Kansas school children. The questionnaire was attached to a cover letter for the parent (or guardian) of each child, which provided general information about the investigation and the rights of the participants.

The questionnaires were copied on different colored paper for easy identification. White forms were given to parents of children who had

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been identified by a physician as having a middle ear problem. These children had failed the school's hearing screening procedures and were referred to a physician for diagnosis. Blue forms were given to parents of children who had passed the school's hearing screening test.

The exact hearing screening procedures might have varied slightly between school districts. The minimum procedures established by state regulations are bilateral pure tone screening at 25 dB HL for the frequencies .5, 1, 2, 4, and 6 kHz (Kansas Department of Education (DOE)/Department of Health and Environment (DHE), 1980). Each child who passed the screening test responded appropriately to the test stimuli. Each child who failed the screening test was rescreened at a later date. If the child failed the rescreening, a pure-tone threshold was obtained. A child was referred for a complete audiometric evaluation and an examination by a physician if the hearing test results showed a loss of 30 dB at two frequencies or 35 dB at one frequency in either ear (KDOE/DHE, 1980). Personnel in some school districts with the appropriate equipment obtained tympanograms as well. The experimental (i.e., diagnosed by a physician with middle ear problems) and control (i.e., passed school's hearing screening) groups, therefore, did not undergo identical subject selection procedures. The subject selection procedures, however, followed the procedures for the identification of middle ear problems in Kansas public schools. The authors determined that these procedures were appropriate for the present survey investigation.

A total of 1600 questionnaires, 800 white forms and 800 blue forms, were divided between the special education directors of each school district in Kansas by the Kansas Department of Education. Ten questionnaires of each color were given to smaller districts; 25 questionnaires of each color were given to larger districts. The directors had been informed, in advance, of the investigation.

Written instructions were provided with the questionnaires to each director. The instructions included:

1. the meaning of the color code;
2. the number of questionnaires provided;
3. the procedures used to code subjects, sex, school district, and age;
4. the procedures to match children from the experimental (i.e., diagnosed with middle ear problems) and control (i.e., passed school's hearing screening test) groups; and,
5. the deadline date and address to return the questionnaires.

Subjects were matched by age, within ± 6 months, and sex. For the statistical analyses, the subjects were grouped by age according to the following categories: less than or equal to 6;6, 6;6 to 8;0, and greater than 8;0 (years;months). Each matched-subjects pair fell within the same age category; no matched pairs crossed age categories. All subjects were se-

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lected, according to the hearing screening and medical exam results, by the staff of the local school district.

RESULTS

A total of 344 questionnaires (21.5%) were returned to the investigators. Of those returned, a total of 238 questionnaires (119 matched pairs) were used in the analyses. One hundred and six questionnaires were excluded from study for a variety of reasons, most often because they lacked an appropriately matched sample. Table 1 shows a breakdown of the 238 subjects by age and sex.

The results of the investigation revealed a significant difference between the two groups for the number of middle ear problems during the last year ($\chi^2 = 96.6$; $df = 3$; $p < .0001$). The members of the experimental group, each of whom was identified by a physician as manifesting a middle ear problem, had significantly more episodes of middle ear problems than the members of the control group, each of whom passed the school's hearing screening test. This finding was important because it was conceivable that some children with a middle ear problem might pass a pure-tone screening, thereby confounding the control group.

There were nonsignificant differences between the two groups on items regarding the presence of smoking in the home ($\chi^2 = 2.84$; $df = 1$; $p > .05$), the number of smokers in the home ($\chi^2 = 2.88$; $df = 2$; $p > .05$), the type of smoking in the home ($\chi^2 = 3.52$; $df = 2$; $p > .05$), and the amount of cigarette ($\chi^2 = 6.55$; $df = 4$; $p > .05$), cigar ($\chi^2 = 0$; $df = 1$; $p > .05$), and pipe ($\chi^2 = 3.23$; $df = 1$; $p > .05$) smoking in the home.

Figure 1 shows the number of homes in each group with the presence and absence of smoking. Cigarette smoking was by far the greatest type of smoking in the home. One hundred and seven respondents indicated that cigarette smoking occurred in the home as compared to 12 respondents who indicated that some other type of smoking occurred.

Figure 2 shows the number of household smokers for each group. Kraemer and colleagues (1983) reported a greater risk for PMEE in children with exposure to two or more household smokers or smoke from more

Table 1. A Breakdown by Age and Sex of the 238 Subjects

Sex	Age group			Total
	< 6;6	6;6-8;0	> 8;0	
M	38	36	60	134
F	30	48	26	104
Total:	68	84	86	238

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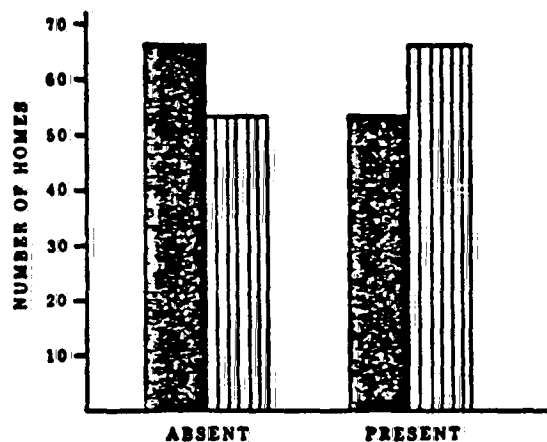
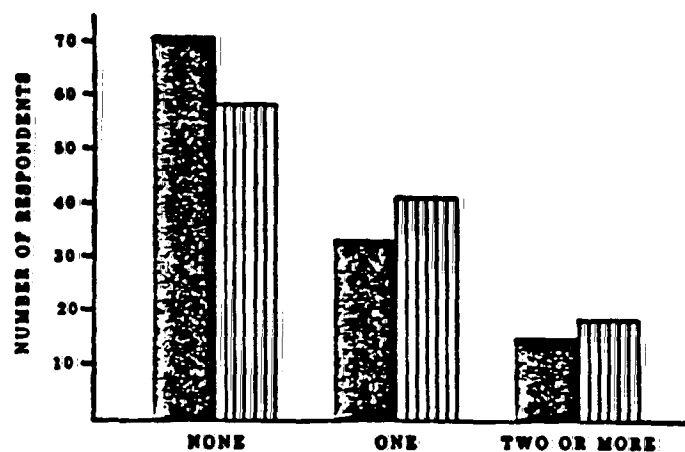


Figure 1. The number of homes with smoking absent and present in the control (solid black) and experimental (black lines) groups.

than three packs of cigarettes per day. A nonsignificant trend is shown in Figure 2 in which the experimental group exhibited more homes with more smokers than the control group. For example, 19 respondents in the experimental group and 15 respondents in the control group reported two or more smokers in the home.

Figure 2. The number of respondents in the control (solid black) and experimental (black lines) groups by the number of household smokers.



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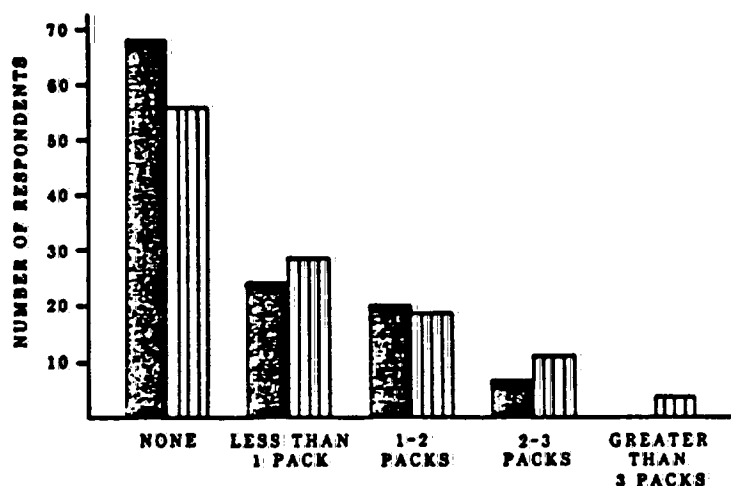


Figure 3. The number of respondents in the control (solid black) and experimental (black lines) groups by the amount of cigarette smoking in the home.

Figure 3 shows the number of respondents in each group by the amount of cigarette smoking in the home. A nonsignificant trend is shown in Figure 3 in which the experimental group reported more smoke in the home than the control group. For example, four respondents in the experimental group and none in the control group reported smoke from more than three cigarette packs per day in the home.

These nonsignificant trends also appeared for cigar and pipe smoking. A greater amount of cigar and pipe smoking was reported for the experimental group. Two respondents in the experimental group and one in the control group reported that cigars were smoked in the home for more than three hours per day. Three respondents in the experimental group and none in the control group reported that pipes were smoked in the home for more than one hour per day.

The results also showed no significant differences in the episodes of middle ear problems by age ($\chi^2 = 8.51$; $df = 6$; $p > .05$) or by sex ($\chi^2 = .41$; $df = 3$; $p > .05$). Apparently, the matching procedures used in this investigation were adequate.

DISCUSSION

Survey investigations traditionally have low response rates. Unfortunately, low response rates may render the results of a survey questionable. The need for follow-up to nonrespondents has been emphasized earlier

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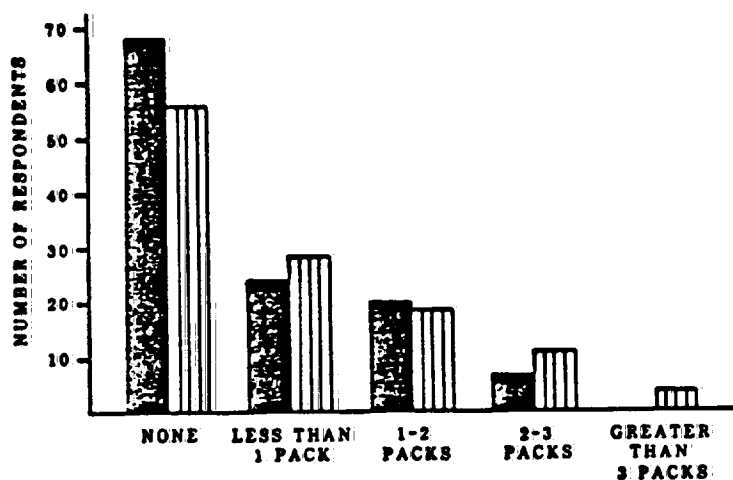


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DISCUSSION

Survey investigations traditionally have low response rates. Unfortunately, low response rates may render the results of a survey questionable. The need for follow-up to nonrespondents has been emphasized earlier

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(Ferber et al., 1980). In the present investigation, the low response rate seemed to result from the failure of the school personnel to distribute and collect the surveys by the established deadline rather than a reluctance of parents to respond. The most common reasons for failing to return the completed questionnaires were that the school personnel forgot to distribute them and that they were too busy with end-of-year responsibilities.

Certainly, if some parents (e.g., smokers) were more likely not to respond than others (e.g., nonsmokers), the survey results would be invalid. The fact that there were nonsignificant differences for the number of smokers in the matched pairs for each group seemed to validate the results. Apparently, smokers and nonsmokers were equally likely to complete the survey.

The results of the present investigation revealed no differences between the experimental and control groups for the presence of smoking, the amount and type of smoking, and the number of smokers in the home. It also was interesting to note a nonsignificant trend for children exposed to very heavy smoking in the home often to have middle ear problems. For these children, a larger sample might have revealed significant differences. Further study of this important health factor is encouraged.

The present study supported the conclusions of Rogers et al. (1984) that exposure to cigarette smoke in the home was not a risk factor for middle ear problems in children. Rogers et al. (1984) reanalyzed previous data from Kraemer et al. (1983) by controlling for the influence of nasal congestion. They suggested that it was the nasal congestion that influenced Kraemer's significant results, not exposure to household cigarette smoking.

Another factor to be considered in the relationship between passive smoking and middle ear problems in children is the effects of air quality. A large body of evidence has indicated a qualitative relationship between air pollution and disease (Perera and Ahmed, 1979). As mentioned earlier, the Seattle, Washington area (where Kraemer's data were collected) has reduced air quality. The state of Kansas has a relatively "clean" air environment. Cigarette smoking and air pollution have been recognized by epidemiological experts as independent factors, which when combined produce an additive and in some cases a synergistic effect (Perera and Ahmed, 1979). The relative elimination of air pollution in the present investigation suggested that tobacco smoke exposure alone might not be as great a risk factor for middle ear problems in children as previously assumed.

It should be pointed out once again that the health risks of smoking, both active and passive, were evident in the literature. The relationship between passive smoking and middle ear problems in children, however, is apparently a complex one. The risks of middle ear problems from exposure to tobacco smoke most probably increase when in combination

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with other risk factors, such as air pollution or nasal congestion, or when the smoke exposure is excessively heavy.

The authors acknowledge the personnel from the many school districts who participated in the investigation. Also, the authors thank Dr. George Milliken, Department of Statistics, at Kansas State University for his assistance in the statistical analyses.

APPENDIX A: QUESTIONNAIRE

I.D. # _____ Age _____

District/Cooperative # _____

Please respond to the following items completely and accurately.

1. For the school-age child identified above, what is the number of episodes of middle ear problems during the last year?
☐ None ☐ 1 to 2 ☐ 3 to 6 ☐ more than 6
2. What was the most recent method of treatment for the middle ear problem?
☐ None ☐ Medication ☐ Surgery
☐ antihistamine ☐ PE tubes (tubes placed in eardrum)
☐ antibiotic ☐ mastoidectomy
☐ antihistamine and antibiotic ☐ other (specify) _____
☐ other (specify) _____
3. How has the number of episodes of middle ear problems changed over the last three years?
☐ No change ☐ Increased ☐ Decreased
4. Does smoking of any kind occur in your place of residence?
☐ Yes ☐ No
If "yes", please complete the remainder of the form.
5. Check each type of smoking that occurs in the place of residence on a typical day (consider both residents and visitors).
☐ Cigarette ☐ Cigar ☐ Pipe
6. Check the number of smokers living in your place of residence.
☐ 1 ☐ 2 ☐ 3 or more
7. Check the total amount of cigarette smoking by all smokers that occurs within your place of residence on a typical day.
☐ None ☐ Less than one pack
☐ At least one pack but less than two
☐ At least two packs but less than three
☐ Three packs or more
8. Check the total amount of pipe smoking by all smokers that occurs within your place of residence on a typical day (double count if two people smoke a pipe at the same time).
☐ None ☐ Less than one hour
☐ At least one hour but less than three hours
☐ At least three hours but less than five hours
☐ Five hours or more
9. Check the total amount of cigar smoking by all smokers that occurs within your place of residence on a typical day (double count if two people smoke cigars at the same time).

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____ antihistamine and antibiotic
____ other (specify) ____ other (specify)
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____ At least one hour but less than three hours
____ At least three hours but less than five hours
____ Five hours or more
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- ___ None ___ Less than one hour
___ At least one hour but less than three hours
___ At least three hours but less than five hours
___ Five hours or more

10. Please add any comments that you feel may be helpful to our investigation. If necessary use the back of this page.

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Tainio, V.M., Savilahti, E., Salmenpera, L, Arjomaa, P, Siimes, M.A., Perheentupa, J. "Risk Factors for Infantile Recurrent Otitis Media: Atopy but Not Type of Feeding" Pediatr Res 23: 509-512, 1988.

ABSTRACT. We followed 183 infants from birth to 2.3 yr of age. Of these infants 28 had recurrent otitis media (ROM), defined as five or more separate episodes of otitis media (OM) during the first 2 yr of life or four such episodes during their 2nd yr. The OM presented during their 1st yr (early onset ROM) in 12 infants and during their 2nd yr (2nd yr ROM) in 16. Eighty infants had no OM and served as a comparison group. Regarding type of feeding, the infants with early-onset ROM did not differ from their age-matched pairs in the comparison group either one month before the first OM or at the time of first episode of OM. Exclusive breastfeeding did not prevent OM and early weaning was not a risk factor for ROM. Atopy was associated with ROM with a relative risk of 1.9 (95% confidence limits 1.2-3.2). It was particularly prevalent among the infants with early-onset ROM, in 67 versus in 25% in the comparison group ($p < 0.01$). During the 2nd yr daily contact with five or more children was associated with ROM with a relative risk of 2.1 (1.3-3.3). The infants with 2nd-yr ROM were in daily contact with more children than the comparison group (mean 11 versus 5; $p < 0.001$). Parental smoking was more frequent among the infants with ROM than in the comparison group (54 versus 33%; $p < 0.05$). In the infants with early-onset ROM plasma concentration of IgM antibodies to cow's milk was highest at the age of 9 months, and the concentration of IgE was highest at the ages of 9 and 12 months. In conclusion atopy, not the type of feeding, is a risk factor for early-onset ROM, and daycare outside the home for ROM during the 2nd yr.

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Risk Factors for Infantile Recurrent Otitis Media: Atopy but Not Type of Feeding

V.-M. TAINIO, E. SAVILAHTI, L. SALMENPERÄ, P. ARJOMAA, M. A. SIIMES, AND
J. PERHEENTUPA

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ABSTRACT. We followed 183 infants from birth to 2.3 yr of age. Of these infants 28 had recurrent otitis media (ROM), defined as five or more separate episodes of otitis media (OM) during the first 2 yr of life or four such episodes during their 2nd yr. The OM presented during their 1st yr (early-onset ROM) in 12 infants and during their 2nd yr (2nd yr ROM) in 16. Eighty infants had no OM and served as a comparison group. Regarding type of feeding, the infants with early-onset ROM did not differ from their age-matched pairs in the comparison group either 1 month before the first OM or at the time of first episode of OM. Exclusive breast-feeding did not prevent OM and early weaning was not a risk factor for ROM. Atopy was associated with ROM with a relative risk of 1.9 (95% confidence limits 1.2–3.2). It was particularly prevalent among the infants with early-onset ROM, in 67 versus in 25% in the comparison group ($p < 0.01$). During the 2nd yr daily contact with five or more children was associated with ROM with a relative risk of 2.1 (1.3–3.3). The infants with 2nd-yr ROM were in daily contact with more children than the comparison group (mean 11 versus 5; $p < 0.001$). Parental smoking was more frequent among the infants with ROM than in the comparison group (54 versus 33%; $p < 0.05$). In the infants with early-onset ROM plasma concentration of IgM antibodies to cow's milk was highest at the age of 9 months, and the concentration of IgE was highest at the ages of 9 and 12 months. In conclusion atopy, not the type of feeding, is a risk factor for early-onset ROM, and daycare outside the home for ROM during the 2nd yr. (*Pediatr Res* 23: 509–512, 1988)

Abbreviations

OM, otitis media
ROM, recurrent otitis media
CM, cow's milk
CMA, cow's milk allergy

OM may occur in early infancy, but its incidence increases rapidly after the age of 6 months (1, 2). In a Finnish follow-up study 5% of infants had OM during the first 6 months of life, 36% during their 1st yr, and 59% during their 2nd and 3rd yr (3). Several risk factors have been identified: daycare outside the home (4), enlarged adenoids (5), feeding in the horizontal position (6), smoking at home (7), and atopy (8, 9), particularly food allergy (9). Some studies suggest a protective effect of breast-

feeding (3, 10, 11) but others detect none (2, 13). Any study of the impact of feeding on morbidity is beset with numerous methodologic limitations (14).

In this prospective study we followed 198 infants throughout the 1st yr of life, carefully recording their feeding regimen, illnesses, and environment. For 183 of the infants similar data were obtained from the parents regarding the 2nd yr by a detailed questionnaire. From these data we analyzed the risk factors for ROM.

MATERIALS AND METHODS

We followed 198 healthy newborns from birth; they were seen at clinic visits at 2, 4, 6, 9, and 12 months of age, and whenever they had any problems regarding feeding, nursing, or illness. At a mean age of 2.3 yr 60 of the infants were examined by one of us (V.-M.T.), and a questionnaire was sent to each family. The questionnaire was returned by 183 families. Data concerning health, feeding, and socioenvironmental factors were recorded at each visit and from the questionnaire (15–17). All medical care during the 1st year was provided by one pediatrician (L.S.). The illnesses during the 2nd yr were treated by physicians chosen by the parents. The services of health center physicians are free of charge. General health insurance covers part of the fees of private practitioners, and additional voluntary insurance usually covers such fees completely. Therefore parents seek medical care for their infants very readily, and pediatric and otologic services are commonly used. A venous blood sample was taken at each clinic visit, and levels of plasma IgE and cows' milk antibodies were measured (15–17). The plasma levels of IgG and IgM CM antibodies are expressed as percentages of a standard plasma with a high level of CM antibodies.

OM was defined as an otoscopic loss of translucency and landmarks, clear inflammation or bulging of, lack of mobility of, or purulent discharge from the tympanic membrane. Infants with OM or ROM were symptomatic.

ROM was defined as the number of separate episodes of OM occurring in the 90th percentile of the whole series of infants during the first 2 yr (five episodes), or in the 95th percentile during the 2nd yr (four episodes). An OM occurring 2 months after a previous OM and after a normal otoscopic finding during the interval was regarded as a separate episode. Early-onset ROM was ROM with the first OM during the 1st yr, and 2nd-yr ROM was ROM with first OM during the 2nd yr.

Atopy. The diagnosis was based on the presence of pruritic dry dermatitis, urticarial eruption, three or more episodes of wheezy bronchitis, or three of the following: rhinorrhea lasting more than 1 month, frequent itching and/or watering of the eyes, two episodes of wheezy bronchitis, gastrointestinal symptoms provoked by foods (16). The most frequent problems were cutaneous.

CMA was diagnosed if skin, respiratory, or gastrointestinal signs developed repeatedly after ingestion of cow's milk and

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disappeared on a cow's milk-free diet, and were provoked by a cow's milk challenge test at hospital.

Feeding. All mothers were encouraged to breast-feed as long as possible. Of the 198 infants, 32 were completely weaned by 3.5 months of age. At 6 months of age 101 and at 9 months 31 infants were still exclusively breast-fed, having no milk formula or other complementary food. The weaned infants followed a standard dietary program including an adapted formula (Tutteli, Valio, Ltd Helsinki; protein concentration 16 g/liter), fruit and vegetables from 3 months of age, and cereals and meat from 5 months. Pasteurized whole cow's milk was substituted for the formula from 9 months. For 98 infants, the most frequent food allergens (eggs, fish, tomatoes, citrus fruit, chocolate, peas, and strawberries) were excluded from the diet until 12 months of age, on the advice given by well baby clinics to the families with a history of atopy.

Socioeconomic background. Of the mothers, 23% had an academic background and another 39% had some other form of higher education; 65% were employed until shortly before the infant's birth, and 38–59% were employed during the follow-up after a maternity leave of 10 months. By self-assessment the economic status was good in 28% of the families, satisfactory in 64%, and unsatisfactory in 8%. The mean housing space was 16 ± 7 (SD) m²/person. There were three single mothers. In 42% of the families the infant was the only child, 22% of families had two children, and 36% three or more children.

Smoking habits and pets. Of the mothers 15% and of the fathers 32% were smokers, and in 36% of the families either one or both smoked. Smoking took place mainly outside the home. Smoking is forbidden in daycare family homes and daycare centers. A pet was present in 20% of the homes.

Daycare and contact with other children. At 12 months of age 62% of the infants were cared for at home by their own mother, 18% in another family-type arrangement, and 20% at a public daycare center. At 24 months the respective numbers were 41, 29, and 24%; 6% had another arrangement. The median number of children in home care was two, in the family-type setting four, and at a daycare center 12.

Statistical analyses. The χ^2 , *t* tests, and multivariate analysis of variance were used for comparisons. Because of skewness of distributions of plasma IgE and cow's milk antibodies, values were analyzed after log transformation. Predictive factors for ROM and for more than one, two, three, four, or five episodes of OM were searched for by stepwise logistic regression. Seventeen variables were tested. The variables were treated as categorical. Some variables were categorical by nature (variables 6, 7, 8, 16, and 17) and others were divided into two categories either in a way that was relevant for the study (i.e., daycare at home or outside the home) or by choosing a cutoff point using the distribution of the whole series of 183 infants (Table 1).

RESULTS

OM. For the study of ROM, the following groups were distinguished among the series of 183 infants: ROM 28 infants, early-onset ROM 12 infants, 2nd-yr ROM 16 infants, and a comparison group of 80 infants who had no OM during their first 2 yr. In addition 151 infants had no OM during their 1st year and 96 during their 2nd yr. In 14 of the 28 infants with ROM adenoidectomy was done and nine had tympanostomy tubes placed. Of the total number of otorhinologic operations in the series, 70% were in infants with ROM.

Upper respiratory tract infections. The frequency of upper respiratory tract infections was not a risk factor for ROM (Table 1). However, during the 1st yr such illnesses were more frequent in the infants with ROM than in the comparison group (6.0 ± 0.6 versus 4.0 ± 0.2 infections, $p < 0.01$). There was no such difference during the 2nd yr (2.8 ± 0.3 versus 3.4 ± 0.5 , respectively).

Feeding. None of the feeding variables tested were risk factors

Table 1. Risk factors for infantile ROM*

	Relative risk + (95% confidence limit)
1. High no. of upper respiratory tract infections (≥ 5 during the first 2 yr of life)†	
2. Short duration of exclusive breast-feeding (≤ 74 days)†	
3. Early regular formula feeding (before the age of 99 days)†	
4. Early complete weaning from breast (before the age of 99 days)†	
5. Early introduction of solid foods (before the age of 131 days)†	
6. Positive family history for atopy	
7. Occurrence of own atopic disease	1.9 (1.2–3.2)
8. Occurrence of CMA	
9. Low educational level of mother: (no higher education)	
10. Low occupational class of mother: (no regular work)	
11. Low social class of family: (lowest of 3 classes)	
12. Small size of home (≤ 45 m ²)†	
13. Daycare outside the home at the age of 12.0 mo	1.9 (1.1–3.2)
14. High no. of child contacts (≥ 5 during yr 2)	2.1 (1.3–3.3)
15. Sleeping arrangements (with siblings or parents)	
16. Smoking of parents (one or both)	
17. Pet at home	

* Relative risk is given only where significantly > 1.0 . ROM was defined as ≥ 5 episodes of OM during the first 2 yr or ≥ 4 episodes during the 2nd yr.

† This limit separates one quartile of the study group.

for ROM (Table 1) or for OM (Table 2). The infants with early-onset or 2nd-yr ROM did not differ from the comparison group in this respect (Tables 3 and 4). The 34 infants with one or more episodes of OM during the 1st yr of life were compared with matched pairs from the comparison group (matched for age, season of birth, smoking of parents, type of daycare, and own atopy) 1 month before the first OM and at the time of first episode of OM. There were altogether three more pairs in whom at the time of the first episode of OM, the infant with OM was weaned more fully than the comparison infant. The infants with early-onset ROM were compared with their matched pairs. Altogether there were no statistical significant differences in these comparisons. Ongoing breast-feeding did not prevent OM; six of the 12 infants with early-onset ROM had the first OM when still exclusively breast-fed and two others when partially breast-fed.

Atopy appeared in 14 infants during the 1st yr and in another 31 during the 2nd yr. It was associated with a 1.9-fold relative risk of ROM (Table 1) and was more common among the infants with ROM than in the comparison group (50 versus 25%, $p < 0.01$). The prevalence of atopy was higher among infants with early-onset ROM than in those with 2nd-yr ROM (67 versus 38%, $p < 0.05$). The infants with early-onset ROM had the highest concentration of plasma IgE at 9 and 12 months of age (Table 5).

CMA was not a risk factor for ROM (Table 1). Seven infants had cutaneous CMA during the 1st yr. They tended to have OM more frequently during the 1st yr than the others (1.5 ± 0.6 versus 0.4 ± 0.1 ; $p < 0.1$). Only two of these seven infants had no OM during the 1st year versus 145 of the other 186 infants ($p < 0.001$). However, only one of the seven infants with CMA had ROM.

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Table 2. Relative risks (and their 95% confidence limits) of OM and its recurrence*

No. of episodes of OM	≥1 (n = 76)	≥2 (n = 55)	≥3 (n = 38)	≥4 (n = 26)	≥5 (n = 17)	ROM (n = 28)
Day care outside the home at age of 12.0 mo	1.7 (1.2-2.3)	1.6 (1.1-2.3)	1.9 (1.3-3.0)	1.8 (1.1-3.0)	1.7 (1.0-2.8)	1.9 (1.1-3.2)
High number of child contacts (>5 during yr 2)		1.4 (0.9-2.0)		1.8 (1.1-2.9)	2.7 (1.5-5.2)	2.1 (1.3-3.3)
Occurrence of own atopic disease					2.2 (1.2-4.2)	1.9 (1.2-3.2)
Smoking of parents (one or both)			1.7 (1.1-2.7)			

* Relative risk is given only where significantly > 1.0. The other 13 variables in Table 1 were not significant risk factors for OM or its recurrence.

Table 3. Feeding parameters in infants with ROM and in the infants without OM; median and 1st and 3rd quartiles are given for age in days*

	Infants with early-onset ROM (n = 12)	Infants with 2nd-yr ROM (n = 16)	Infants without OM (n = 80)
First exposure to cow's milk	242 (78-258)	98 (36-281)	240 (82-291)
Start of regular formula feeding	242 (180-278)	258 (80-290)	251 (111-294)
Complete weaning from breast	335 (186-404)	238 (98-347)	286 (111-354)
Introduction of solid foods	185 (133-233)	176 (132-239)	190 (134-235)

* There were no statistically significant differences between these groups, or between all infants with and those without ROM.

Table 4. Prevalence of exclusive breast-feeding among infants with ROM and infants without OM*

Age (mo)	Infants with early-onset ROM (n = 12) (%)	Infants with 2nd-yr ROM (n = 16) (%)	Infants without OM (n = 80) (%)
2	92	75	81
6	58	50	60
9	0	31	18

* There were no statistically significant differences between these groups or even between all infants with and without ROM.

Cow's milk antibodies. The mean levels of IgG cow's milk antibodies were similar in the ROM group and the comparison group. At 12 months of age a higher proportion of infants with ROM than of the comparison group (22 versus 6%, $p < 0.05$) had supranormal (>2.0 SD) levels of IgG cow's milk antibodies. At 9 months of age the infants with early-onset ROM had a higher mean level of IgM cow's milk antibodies than the infants with 2nd-yr ROM (58 versus 12%, of the standard plasma, $p < 0.05$).

Socioeconomic background. The group with ROM did not differ from the comparison group in the educational level of the mother or the economic status of the family. The mean absolute and relative size of the home was similar, as was the mean size of the family.

Number of child contacts and day-care. The number of daily child contacts during the 2nd yr was a predictive factor for ROM. The relative risk was 2.1 (Table 1) if the number of child contacts was five or more. During their 2nd yr the infants with 2nd-yr ROM had daily contacts with a mean of 11 versus five children for the infants with early-onset ROM and five for the comparison group ($p < 0.001$). Daycare outside the home at the age of 1.0 yr was also a risk factor for ROM (Table 1), even for the first

episode of OM (Table 2). The proportion of infants having daycare outside the home during both their 1st and 2nd yr was higher among the infants with ROM than among those of the comparison group (59 and 69% versus 24 and 44%; $p < 0.05$). The same was true for those attending a daycare center during their 2nd year (44 versus 18%, $p < 0.05$). However, 10 of the 12 infants with early-onset OM had the first OM when still being taken care of at home. Ten of 16 infants with 2nd-yr ROM had daycare outside the home when OM presented.

Smoking and pets. Of the parents, 55% smoked in the ROM group versus 33% in the comparison group ($p < 0.05$). There was no such significant difference between the groups in the proportion of homes with a pet (16 versus 20%).

DISCUSSION

We noticed a rapid increase in the incidence of OM from 22% during the infants' 1st yr to 48% during their 2nd yr. The incidence of OM is highest during the first 2 yr of life (1-2, 18). Our values were close to those reported (2, 3, 18). There are no accepted criteria for ROM; our definition (five or more episodes during the first 2 yr or four or more during the 2nd yr) resulted in an incidence of 15%. A similar incidence (13%) was found in another Finnish study (3), but much higher values (30%) have been reported (1, 2).

We found different risk factors in infants with early-onset and 2nd-yr ROM. Most of the infants with early-onset ROM had atopy and the mean plasma level of IgE was higher in these infants than in the infants with 2nd yr ROM and those without OM. This association with atopy has been noted earlier in regard to secretory OM (19, 20), but has recently been disputed (3, 21). The majority of infants with early-onset ROM were partially or exclusively breast-fed, were cared for at home, and had a small number of daily child contacts at the time of the first episode of OM. In contrast, the infants with 2nd-yr ROM did not differ from the comparison group in the frequency of atopy. They had a large number of daily child contacts and were taken care outside the home during the 2nd yr of life; these were significant risk factors for ROM and for the recurrence.

Smoking by the parents may irritate the respiratory mucosa and so predispose to ROM (7, 18, 23) but today parents seem to be aware of this risk and avoid smoking at home or at least in the vicinity of the infant. Although parental smoking was not a risk factor for ROM, there were more smokers among parents of the infants with ROM than in the comparison group.

In our prospective study we tried to control and record all known confounding factors and we had detailed information about the feeding of the infants. We could study the simultaneous effect of many factors and identify independent risk factors for ROM by logistic regression analysis. These turned out to include no feeding variables. The mean durations of exclusive breast-feeding and of breast-feeding in general were similar in the infants with ROM and the comparison group. Thus prolongation of exclusive breast-feeding does not seem to afford added protection. All the infants were initially breast-fed and may have benefitted from this concerning the propensity toward ROM.

Table 5. Plasma IgE concentrations (IU/ml) in infants with early-onset and 2nd-yr ROM and infants without OM (geometric mean and 95% confidence limits are given)

Series	IgE		IgE		IgE	
	at 6 mo	n	at 9 mo	n	at 12 mo	n
Infants with early-onset ROM	3.2 (1.3-7.9)	12	5.5 (1.6-18.7)	9	10.8 (3.9-30.0)	12
Infants with 2nd-yr ROM	1.3 (0.5-3.1)	8	1.3 (0.6-2.9)	10	1.8 (0.7-4.7)	12
Infants without OM	3.3 (2.2-5.0)	63	3.9 (1.8-8.0)	65	6.1 (4.3-8.8)	77

Significant differences between groups are indicated: * $p < 0.05$; † $p < 0.01$.

However, our study does not allow an evaluation of benefits of early breast-feeding. Neither short nor prolonged breast-feeding were risk factors for infantile atopy in our series (16). The total level of IgA was lower in the milk of the mothers whose infants became allergic to cow's milk than in mothers with nonallergic infants (24). Thus the quality of the breast milk may be more important in conferring resistance to disease than the duration of breast-feeding.

Cow's milk has been claimed to cause recurrence of OM in infancy either as an allergen (9) or as a direct irritant of the nasopharyngeal tubes in horizontal feeding (6). OM was more common in the infants with CMA than in the others, but only one of the infants with CMA developed ROM. Probably early detection of CMA with subsequent elimination diet and otorhinologic operations averted the cycle of infections. Another finding suggesting that cow's milk plays a role in ROM in some infants is the increased level of IgM antibodies to cow's milk in the plasma of these infants and the increased prevalence of supra-normal levels of IgG antibody to cow's milk.

Our findings indicate that infantile ROM is associated with a number of predisposing factors. In some infants immune reactions are associated with cow's milk feeding. In infants developing ROM the most important risk factor in the 1st yr was their own atopy; in contrast to daycare outside the home and a large number of child contacts in the 2nd yr.

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~~CONFIDENTIAL~~

Strachan, D.P., Jarvis, M.J., Feyerabend, C. "Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children" Br Med J 298: 1549-1552, 1989.

This cross-sectional observational study was designed to assess the contribution of passive smoking to the development of middle ear underpressure and effusion. The subjects were 892 children aged 6.5-7.5 years taken from one-third of the primary schools in Edinburgh. Satisfactory tympanograms were obtained for 872 subjects, and results of assay of salivary cotinine concentrations were available for 770 children. Both measures were available in 736 of the original 892 children. The aim of this study was to determine if there was a correlation between the prevalence of middle ear underpressure and effusion and the salivary cotinine levels in the children. The authors reportedly found that there was a trend towards more abnormal tympanometric findings with increasing cotinine levels. The conclusion of the authors was that "[t]he results of this study are consistent with those of case-control studies of children attending for an operation to relieve middle ear effusion" and that "about one-third of the cases of middle ear effusion in this study were statistically attributable to exposure to tobacco smoke." The investigators recommend that "the disease should be added to the list of recognized hazards associated with passive smoking."

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Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children

D P Strachan, M J Jarvis, C Feyerabend

Abstract

Objective—To assess the contribution of passive exposure to tobacco smoke to the development of middle ear underpressure and effusion.

Design—Cross sectional observational study.

Setting—One third of the primary schools in Edinburgh.

Subjects—892 Children aged 6½ to 7½ were examined, and satisfactory tympanograms were obtained in 872. Results of assay of salivary cotinine concentrations were available for 770 children, and satisfactory tympanograms were available for 736 of these.

End point—Correlation of the prevalence of middle ear underpressure and effusion with concentrations of the marker of nicotine, cotinine, in the saliva of the children.

Measurements and main results—Middle ear pressure and compliance were measured in both ears by impedance tympanometry. Salivary cotinine concentrations were assayed by gas-liquid chromatography. Cotinine concentrations increased with the number of smokers in the household. Girls had higher concentrations than boys, and children living in rented housing had higher concentrations than those living in housing owned by their parents. There was a trend towards more abnormal tympanometric findings with increasing cotinine concentration, the odds ratio for a doubling of the cotinine concentration being 1.14 (95% confidence interval 1.03 to 1.27). After adjustment for the sex of the child and housing tenure the odds ratio for a doubling of the cotinine concentration was 1.13 (1.00 to 1.28).

Conclusions—The results of this study are consistent with those of case-control studies of children attending for an operation to relieve middle ear effusion. They indicate that the disease should be added to the list of recognised hazards associated with passive smoking. About one third of the cases of middle ear effusion in this study were statistically attributable to exposure to tobacco smoke.

Introduction

Middle ear effusion (glue ear) is the commonest reason for admitting young children for an operation,¹ but little is known about its cause.² Case-control studies of children admitted for insertion of a grommet have shown an increased risk associated with the presence of smokers in the household,^{3,4} particularly in children who had been exposed to high levels of tobacco smoke.⁵ Criteria for referral and admission for middle ear effusion seem to be determined substantially by the "health culture" of the family⁶ and by local clinical practice, which may in turn be affected by the availability of services.⁷ Thus the interpretation of studies based on patients in hospital is complicated by selection bias, which may result in either a spurious relation with parental smoking or an underestimate of a true effect.

Five studies of children in the general population have reported on the association between middle ear effusion and passive exposure to smoke.⁸⁻¹² Only

Iversen *et al* found a significant association, and their results suggested that the risk associated with passive smoking increased with age.⁸ If this is so it might explain the negative results of the other studies, which were based on children aged less than 5 years old.⁹⁻¹²

Both middle ear effusion and exposure to tobacco smoke can be measured objectively. Since its introduction some 20 years ago¹³ impedance tympanometry has been widely used as a diagnostic and screening tool in young children, and its relation to fluid in the middle ear has been validated in patients attending for myringotomy.^{14,15} Cotinine, an important metabolite of nicotine, is the most suitable marker to measure passive exposure to tobacco smoke. It is specific, has a half life of about 20 hours, and can be assayed in concentrations as low as 0.57 nmol/l (0.1 ng/ml) by gas-liquid chromatography.¹⁶ Salivary concentrations of cotinine are roughly in proportion to those in blood and have been used to measure exposure to environmental tobacco smoke in adults^{17,18} and adolescents.^{19,20}

We investigated the relation between exposure to smoke and middle ear disease in a sample population of 7 year old schoolchildren who were participating in a survey of the effects of the home environment on respiratory health.²¹

Subjects and methods

A sample of one in three primary schools in Edinburgh was chosen at random, and the parents of all children in the third primary class (aged 6½-7½ years in September 1986) were contacted by postal questionnaire. This asked about respiratory symptoms and housing conditions relating to the child; more details are reported elsewhere.²² The current or latest occupation of the head of the household was coded to a social class according to the registrar general's classification of occupations.²³ Written parental consent to clinical tests was requested, and ethical approval for the study was obtained from Lothian Health Board and Lothian Regional Council's education department.

Clinical tests were performed at the schools during January to June under the supervision of DPS. Middle ear pressure and compliance, the volume of the ear canal, and the relative gradient of the tympanometric curve were measured in both ears with a Microlab Earscan configured for impedance measurements (Micro Audiometrics, Florida, United States). This uses a probe tone of 226 Hz at 85 db and sweeps from 200 to -312 daPa at 100 daPa/s. The children were asked to swallow a sip of water immediately before the measurement was made to ensure that patent eustachian tubes would be ventilated. Table 1 shows the types of tympanograms, defined on the basis of the modification of Jerger's original classification²⁴ that was proposed

TABLE 1—Types of tympanograms according to Fiellau-Nikolajsen²⁴

Type	Middle ear pressure (daPa)	Gradient (%)	Interpretation
A	200 to -99.9	>10	Normal
C1	-100 to -199.9	>10	Mild underpressure
C2	-200 to -312	>10	Severe underpressure
B	No peak	<10	Middle ear effusion

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and validated by Fiellau-Nikolajsen.¹ To characterise each child the tympanogram obtained on examination of the more abnormal ear was used in the analysis.

The children were asked to collect saliva in their mouths and to spit into a clean plastic container. A sample of at least 1 ml was frozen within eight hours after collection for assay of cotinine concentration by gas-liquid chromatography.² Statistical analyses were performed by the statistical analysis system (SAS),^{3,4} and logistic regression models were fitted by the generalised linear interactive modelling system (GLIM).⁵ Tests for trend with one degree of freedom used the procedure proposed by Mantel⁶ and implemented for stratified tabulations in the FREQ procedure in SAS.⁷

Results

The parents of 1095 children were sent a questionnaire, and 941 (86%) consented to their child being examined clinically. Twenty of these children left school before the survey was carried out, and a further 20 were included in pilot studies. Of the remaining 901 eligible children, 892 (99%) were examined, and satisfactory tympanograms were obtained for one or both ears in 872. In 23 children results were obtained for only one ear, but these were included in the analysis.

Table II shows the relation between findings on tympanometry and the sex of the child, social class, housing tenure, and number of smokers in the household. There was no significant difference in middle ear pressure with sex or social class (when this was known), but the prevalence of middle ear effusion (type B tympanogram) was higher in girls and among

children of unknown social class. There was a significant trend towards abnormal tympanograms in the children whose parents were smokers, and the prevalence of effusion increased with the number of smokers in the household (χ^2 for trend in proportions = 4.15, $df=1$, $p<0.05$). There was a similar trend, which was of borderline significance ($p=0.051$), associated with rented housing.

The results of the salivary cotinine assay were available for 770 children (405 from non-smoking households, 241 from households with one smoker, and 124 from households with two or more smokers). Table III shows the distributions of salivary cotinine concentrations in these three groups. A total of 109 (27%) children from households with no smokers had concentrations below the limit of the assay (0.57 nmol/l), whereas only one child from a household with one or more smokers had no detectable salivary cotinine. Six children, five of them from households with only one smoker, had concentrations >82 nmol/l, a suggested cut off point to distinguish between smoking and non-smoking adults and adolescents.^{8,9} These values were 93.1, 97.1, 106.2, 119.3, 144.8, and 205.0 nmol/l.

Table IV shows the relation between cotinine concentrations, sex of the children, and housing tenure within groups with similar numbers of smokers in the home.

TABLE IV—Geometric mean salivary cotinine concentrations* (nmol/l) in 770 children aged 7 according to sex of child, housing tenure, and number of smokers in household. Numbers of children are given in parentheses

No of smokers in household	Tenure of housing			
	Owned		Rented	
	Boys	Girls	Boys	Girls
0	0.85 (176)	1.02 (161)	3.01 (35)	8.63 (33)
1	5.62 (67)	6.53 (74)	17.04 (53)	25.95 (47)
≥ 2	15.61 (28)	17.04 (33)	21.47 (30)	34.36 (33)

* Undetectable concentrations were recorded as 0.28 nmol/l.

TABLE II—Prevalence (%) of types of abnormalities on tympanometry of the more abnormal ear in 872 children aged 7 according to sex of child, socioeconomic state, housing tenure, and number of smokers in household. Numbers of children are given in parentheses

	Middle ear pressure (daPa)				χ^2 Trend*
	100 to -100 (type A)	-200 to -100 (type C1)	-300 to -200 (type C2)	No peak (type B)	
Sex:					
Girls	63.1 (275)	17.0 (74)	12.4 (54)	7.6 (33)	0.60
Boys	62.2 (271)	17.2 (75)	9.4 (41)	11.2 (49)	
Social class of head of household:					
I	63.9 (62)	16.5 (16)	12.4 (12)	7.2 (7)	0.00
II	63.9 (145)	14.5 (33)	14.5 (33)	7.1 (16)	
IIIN	62.4 (104)	21.4 (37)	5.2 (9)	11.0 (19)	
IIIM	65.2 (118)	17.7 (32)	6.6 (12)	10.5 (19)	
IV/V	62.9 (66)	14.3 (15)	17.1 (18)	5.7 (6)	
Unknown†	52.8 (47)	18.0 (16)	12.4 (11)	16.9 (15)	
Tenure of housing:					
Owned	64.6 (396)	16.3 (100)	10.6 (65)	8.5 (52)	3.80
Rented	57.8 (147)	18.5 (47)	11.8 (30)	11.8 (30)	
No of smokers in household:					
0	63.9 (292)	17.3 (79)	10.7 (49)	8.1 (37)	3.97‡
1	63.3 (169)	16.5 (44)	10.9 (29)	9.4 (25)	
≥ 2	56.4 (79)	17.1 (24)	12.1 (17)	14.3 (20)	
Fifths of salivary cotinine (nmol/l):					
<0.57	64.8 (70)	15.7 (17)	12.0 (13)	7.4 (8)	7.01§
0.57–	72.6 (130)	13.4 (24)	8.9 (16)	5.0 (9)	
2.27–	65.4 (104)	20.8 (33)	5.7 (9)	8.2 (13)	
7.38–	61.0 (89)	17.8 (26)	6.9 (10)	14.4 (21)	
>19.9	58.3 (84)	16.7 (24)	12.5 (18)	12.5 (18)	

* $df=1$.

† Head of household was a student, a member of the armed forces, or had never been employed; this group was excluded from the test for linear trend.

‡ $p<0.05$; § $p<0.01$.

TABLE III—Distribution of salivary cotinine concentrations according to number of smokers in household

No of smokers in household	Salivary cotinine (nmol/l)				
	Minimum	First quartile	Median	Third quartile	Maximum
0 ($n=405$)	ND	ND	1.1	2.3	36.9
1 ($n=241$)	ND	4.5	10.2	22.7	205.0
≥ 2 ($n=124$)	2.3	12.5	25.0	37.5	97.1
Total ($n=770$)	ND	0.6	4.0	16.5	205.0

ND = None detected (<0.57 nmol/l).

In view of the skewed nature of the distributions for cotinine concentrations the table gives geometric mean values. For logarithmic transformation undetectable concentrations were treated as 0.28 nmol/l. Female sex and rented housing were independently and consistently associated with higher cotinine concentrations given the same number of smokers in the household. These effects were apparent even in non-smoking households, and the difference with sex was particularly pronounced among children from rented homes.

Satisfactory tympanograms were obtained for 736 of the 770 children for whom we had data on salivary cotinine concentrations. When cotinine concentrations were grouped in fifths of the distribution there was a highly significant trend towards more abnormal tympanograms in the children with higher concentrations (table II). In view of the associations between cotinine concentrations and sex of the child and housing tenure and the modest effect of these factors on the prevalence of middle ear effusion the relation between salivary cotinine concentrations and abnormal tympanograms was analysed further by multiple logistic regression. Presence or absence of effusion (type B tympanogram) was treated as a dichotomous outcome variable. To investigate the form of the dose-response relation in more detail the data on cotinine concentrations were fitted as a continuous explanatory variable. The logarithm of the cotinine concentration was found to give the best fit, its relation to the prevalence of type B tympanograms being close to linear on a logarithmic scale (χ^2 for inclusion of quadratic term = 0.0000, $df=1$).

In single factor models the odds ratio for female sex was 1.53 (95% confidence interval 0.92 to 1.98), and

for rented housing it was 1.43 (0.84 to 2.42). The effect of the logarithm of the cotinine concentration in a single factor model was significant ($\chi^2=6.60$, $df=1$, $p<0.02$), and the odds ratio for a doubling of salivary cotinine concentration was 1.14 (1.03 to 1.27). In a joint model including all three factors the effects of sex and logarithm of the cotinine concentration changed little, but there was an appreciable reduction in the odds ratio for children living in rented housing, suggesting that passive exposure to smoke accounted for much of the effect of rented housing in the single factor models. The adjusted odds ratios were 1.46 (0.87 to 2.44) for female sex, 1.03 (0.55 to 1.91) for rented housing, and 1.13 (1.00 to 1.28) for a doubling of salivary cotinine concentration. The effect of the logarithm of the cotinine concentration remained significant in the joint model ($\chi^2=4.14$, $df=1$, $p<0.05$). Further adjustment for parental social class, number of people living in a room, gas cooking, and the presence of damp walls in the home made no substantial difference to the coefficient for the logarithm of the cotinine concentration.

The linear relation between the logarithm of the cotinine concentration and the prevalence of middle ear effusion on a logit scale implied that the prevalence odds were proportional to a power of the cotinine concentration, the power exponent being the coefficient (logarithm of the odds ratio) for the logarithm (base e) of the cotinine concentration in the logistic model. The data suggested that the odds ratios for type B tympanograms after adjustment for sex and housing tenure relative to children with undetectable cotinine concentrations would be approximately 1.7 at 5.7 nmol/l (1 ng/ml) and 2.3 at 28.4 nmol/l (5 ng/ml). Thus, even low levels of passive exposure to smoke may have substantial effects on the prevalence of middle ear effusion. The model predicted that in a population of the same distributions of age, sex, and tenure in which all children had undetectable cotinine concentrations the prevalence of type B tympanograms would be approximately 5.8%. As the observed prevalence was 9.4% at least one third of the cases of middle ear effusion in this age group may have been attributable to passive smoking.

Discussion

We believe that this is the first study to report biochemical data on passive exposure to smoke in primary school children. The age group chosen was young enough to exclude regular active smoking, but some of the higher concentrations of salivary cotinine observed were greater than could reasonably have been attributed to passive exposure. These high concentrations may indicate experimentation with cigarettes, even at this early age. None of the six children with cotinine concentrations above 82 nmol/l, however, had middle ear effusion (five had normal (type A) tympanograms), so their inclusion in the analysis will have tended to diminish any effects attributed to passive exposure to smoke rather than to generate a spurious effect.

As expected, cotinine concentrations were related to the number of smokers in the household, but equally striking was the variation with sex of the children and housing tenure within groups with the same numbers of smokers. Even among the children from non-smoking households cotinine concentrations were higher in those living in rented accommodation. This suggests that considerable exposure to smoke occurs outside the home, which is strongly related to social factors. When tenure and number of smokers were controlled for girls had higher salivary cotinine concentrations than boys. This may reflect differences in cotinine metabolism or in activity patterns, boys being

perhaps more likely to play outdoors or away from adults who smoke. No difference with sex has been found in older children.¹¹

The prevalence of abnormalities on tympanometry in this population of 7 year old children is consistent with previous reports.^{12,13} Tympanometry was performed only once, and many of the abnormalities detected, including middle ear effusion, tend to resolve spontaneously.¹⁴ This population survey probably included only a few cases of persistent disease in which an operation would be indicated. The findings are therefore complementary to, rather than directly comparable with, case-control studies of children admitted to hospital.¹⁵ They do, however, relate to an age group close to the peak age for admission for an operation for middle ear effusion.¹¹

Our results show a significant relation between salivary cotinine concentrations and disease of the middle ear, whether a range of abnormal tympanograms, or tympanograms with and without a definable peak (taken to indicate effusion) are considered. These associations were probably not due to bias because the measurements were objective and the laboratory analysts were blind to the tympanometric findings. Adjustment of the crude estimates of the effect of sex and housing tenure on cotinine concentrations indicated some confounding by these factors, but confounding by socioenvironmental factors probably did not persist in the final model. The coefficient for housing tenure in the joint model was small, and further adjustment for social class and a range of more specific housing characteristics made little difference to the results.

Salivary cotinine concentrations relate only to passive exposure to smoke in the previous two or three days, but Jarvis *et al* reported that over one year concentrations in non-smoking adolescent girls was reasonably stable.¹⁶ Nevertheless, variation in exposure from week to week limits the reliability of a single measurement, and the true association between passive smoking and middle ear effusion is therefore underestimated in our data.¹¹

The relation between passive exposure to smoke and middle ear effusion in the present study is more likely to be causal than due to chance, bias, or confounding factors. The common mechanism in the development of serous otitis media is considered to be loss of patency of the eustachian tube, to which anatomical factors, impaired mucociliary function, and upper respiratory infection or allergy may contribute.¹⁷ Passive smoking may increase the risk of blockage of the eustachian tube in three ways: by directly impairing mucociliary function; by causing congestion of the soft tissues of the nasopharynx; or by predisposing people to upper respiratory infection. Because this was a study of the prevalence of middle ear effusion we cannot draw conclusions about whether exposure to smoke influences the incidence or the persistence of the disease.

Concern has been expressed recently that the documented risks of passive smoking have not included middle ear effusion.¹⁸ In view of the important burden on the health service imposed by this disease¹⁹ and suspicions of its long term effects on linguistic and cognitive development²⁰ middle ear effusion in children should be regarded as one of the more important hazards attributable to environmental tobacco smoke.

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Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly

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Abstract

Objective—To investigate the relation between mortality and treated systolic and diastolic blood pressures.

Design—Randomised double blind placebo controlled trial. Mortality in the two treatment groups was examined in thirds of treated systolic and diastolic blood pressures.

Patients—339 And 352 patients allocated to placebo and active treatment, respectively. The groups were similar at randomisation in sex ratio (70% women), mean age (71.5 years), blood pressure (182/101 mm Hg), and proportion of patients with cardiovascular complications (35%).

Measurements and main results—In the placebo group total mortality rose with increasing systolic pressure whereas it had a U shaped relation with diastolic pressure, the total lowest mortality being in patients in the middle third of the distribution of diastolic pressure. In the group given active treatment total mortality showed a U shaped relation with systolic pressure and an inverse association with treated diastolic pressure. In both groups cardiovascular and non-cardiovascular mortality followed the same trends as total mortality. The increased mortality in the lowest thirds of pressure was not associated with an increased proportion of patients with cardiovascular complications at randomisation or with a fall in diastolic pressure exceeding the median fall in pressure in each group. In contrast, patients in the lowest thirds of pressure showed greater decreases in body weight and haemoglobin concentration than those in the middle and upper thirds of pressure.

Conclusions—In patients taking active treatment total mortality was increased in the lowest thirds of treated systolic and diastolic blood pressures. This increased mortality is not necessarily explained by an exaggerated reduction in pressure induced by drugs as for diastolic pressure a U shaped relation also existed during treatment with placebo. In addition, patients in the lowest thirds of systolic and diastolic pressures were characterised by decreases in body weight and haemoglobin concentration, and the patients in the lowest thirds of diastolic pressure taking active treatment also by an increased non-cardiovascular mortality, suggesting some deterioration of general health.

Introduction

Several large studies of hypertension have recently been reviewed.^{1,2} The observation in these studies of a J shaped relation between the risk of myocardial infarction and treated blood pressure^{3,4} has led to the suggestion that a reduction of pressure induced by drugs might cause as well as prevent myocardial ischaemia.^{1,5,6} None of the studies was placebo controlled, and other large hypertension-mortality intervention trials have either not confirmed^{7,8} or not reported^{9,10} this J shaped relation. In the international prospective primary prevention study in hypertension all patients received active drugs but patients with overt ischaemic heart disease were excluded¹¹; there was no evidence for a J curve. In contrast, Coope and Warrender found that total mortality and deaths from myocardial infarction showed a J shaped relation with the diastolic pressure attained in elderly patients with

European Working Party on High Blood Pressure in the Elderly
Collaborating centres are listed at the end of this paper. Manuscript prepared by J Staessen and A E Fletcher

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undecided. I found similar responses amongst a random sample of 1000 general practitioners in New Zealand: 22% reported that informed consent for testing was not at all important and 4% were undecided. I, too, found that years since graduation was a significant variable as was the number of patients requesting an HIV test. Younger doctors and those with the most requests for tests believed more strongly in informed consent.

In addition I examined attitudes to anonymous testing and to confidentiality. Anonymous testing, although recommended and widely practised in New Zealand, was disagreed with by 28% of the sample, including 7% who disagreed strongly. In fact, only 41% agreed with it, the remainder being neutral. Attitudes to confidentiality were shown by the doctors' responses to questions on sharing information about patients with AIDS. Sixteen per cent of the doctors would give such information to reception staff, and the same proportion would give it to colleagues outside the practice. Women doctors were less likely to do this than men.

It is worrying that the findings of this study and those of Dr Shapiro show some indifference to major issues regarding patients' rights such as informed consent and anonymous testing. This is particularly and given the crucial role that general practitioners will have in the future in caring for those with AIDS or HIV infection and their families. Such indifference will inevitably lead to mistrust on the part of patients and to a reluctance to seek help from general practitioners when it is needed. Future efforts in educating general practitioners about HIV must address these matters.

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1 Shapiro JA. General practitioners' attitudes towards AIDS and their perceived information needs. *Br Med J* 1985;291:1563-6. (10 June.)

Passive smoking and middle ear effusion in children

SIR,—Dr D Strachan and colleagues presented an interesting report on the possible association of passive smoking with otitis media with effusion,¹ but there are three points that need addressing before their conclusions can be reached.

Eustachian tube dysfunction is extremely common in children and gives rise to negative middle ear pressure and middle ear effusion. The prevalence of middle ear effusion varies inversely with age, but there is also a marked seasonal variation, possibly related to a similar variation in upper respiratory tract infections.² The authors have quite rightly confined themselves to a single age group, but they carried out their tests over a period from January to June. Those tested earlier should have a higher rate of abnormal results, but this is not taken into account in the analysis.

Perhaps more importantly they fail to indicate whether the children had already had ear, nose, and throat operations (which at the age of 7 must be a considerable percentage) or whether there were other important factors such as cleft palate or Down's syndrome.

As otolaryngologists we deplore the use of tympanometry alone in the diagnosis of middle ear disease. It is a useful screening test, but in the presence of an abnormal finding we believe otoscopy must be performed. Frequently an obvious cause for the flat tympanogram such as wax, perforation, or even a grommet will be found. Dr Strachan and colleagues unfortunately do not seem to have checked their findings with otoscopy.

A possible indicator of this fault can be found in

their numbers of abnormal tympanograms with increasing cotinine concentrations. There seems to be a trend relating increasing incidence, but flat tympanograms to cotinine concentration, but there is no such trend with negative middle ear pressure. If one assumes that the same pathological process causes both negative middle ear pressure and middle ear effusion through dysfunction of the eustachian tube then the association between passive smoking and middle ear effusion is quite likely to be spurious.

It seems a pity that a paper written by an epidemiologist, a psychiatrist, and a chemist about an ear, nose, and throat condition should not have had the very necessary skills of an otolaryngologist to validate its findings.

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1 Strachan DP, Jarvis MJ, Fryback DG. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br Med J* 1989;299:1549-52. (10 June.)
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AUTHORS' REPLY.—Impedance tympanometry may not be the definitive diagnostic test for middle ear diffusion, but most previous epidemiological surveys have relied on this technique. Tympanometric measurement of the physical volume of the ear canal guards against the common sources of error. High values (>2.0 ml) indicate a perforated eardrum or patent ventilation tube, and in the seven children with such abnormality we conservatively chose to analyse the tympanogram from the other ear. No results were recorded from ears with blockage of the probe or low physical volume (<0.5 ml) suggesting wax. It is unlikely that flat tympanograms attributable to impacted wax could have generated a spurious association with passive exposure to smoke.

Children whose tonsils or adenoids had been removed ($n=104$) were at substantially higher risk of middle ear effusion (22% v 8%). Such a history was unrelated to the presence of smokers in the household (12% v 13%), so it is unlikely that previous surgical treatment affected the observed relation between middle ear effusion and passive exposure to smoke.

Different relations of passive smoking to type C and type B tympanograms might be expected if tobacco smoke affects the persistence of effusions rather than their incidence. In fact, normal (type A) tympanograms were less common in the children with higher cotinine concentrations, so that among the children without effusion there was a slightly higher risk of reduced middle ear pressure with heavy exposure to smoke (table II in our paper).

Month of examination would not affect the association between tympanometric findings and the number of smokers in the household, which was ascertained by a simultaneous questionnaire survey, but it was a potential confounding variable in our analysis of middle ear effusion and salivary cotinine concentrations. The prevalence of type B tympanograms was higher among children tested in January or February (12%) than in March or April (10%) and May or June (7%). After adjustment for sex, housing tenure, and number of smokers in the household the geometric mean salivary cotinine concentration in January and February was approximately double that in May and June. Nevertheless, the relation between middle ear effusion and the logarithm of the cotinine concentration remained significant after adjustment for month of examination (odds ratio per doubling 1.12, 95% confidence interval 1.01 to 1.25, $\chi^2=4.30$, $df=1$). Indeed, after adjustment for log cotinine the trend in prevalence by month of examination was non-significant (χ^2 (trend)=

1.07, $df=1$). Greater indoor exposure to tobacco smoke during the winter may contribute to the seasonal variation in prevalence of middle ear effusion.

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SIR,—I agree with Dr D P Strachan and colleagues that middle ear effusions in children should be recognised as one of the hazards of passive smoking.¹ It has been recognised for some time that passive smoking may have deleterious effects on the respiratory tracts of children. It is only recently that the adverse effects of passive smoking on the middle ear have been reported.

Not only is passive smoking in children associated with a higher than expected incidence of middle ear effusions and abnormal results of tympanometry² but these children are put at an increased risk of undergoing surgery for the condition. There is an increased incidence of grommet insertion and adenotomy in children whose parents smoke. Such children are twice as likely to require adenotomy, and their chance of requiring grommet insertion is increased by half.³

It is important to impress upon smoking parents that they may be subjecting their children not only to a greater risk of middle ear effusions but also to an increased likelihood of surgical intervention for the condition with the possibilities of both physical and psychological complications.

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1 Strachan DP, Jarvis MJ, Fryback DG. Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. *Br Med J* 1989;299:1549-52. (10 June.)
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Transurethral prostatic resection: a safe operation

SIR,—I was intrigued by Mr G Williams and colleagues' use of an expandable metal mesh stent for treating prostatic obstruction in patients considered unfit for transurethral prostatic surgery.¹ I was surprised, however, by their statement that the mortality associated with transurethral resection of the prostate has "led to a search for less invasive treatments," thus prompting this innovation.

Equally surprisingly, Mr Williams and colleagues were presented (in a short time, it would seem) with nine patients who were considered unfit for prostatic resection and hence were offered a stent as alternative treatment. Although the authors did not indicate the timespan over which these cases were collected, it could not have been very great as the first urological use of these stents was reported only in 1988. Accordingly the nine patients considered unfit for transurethral resection would seem to represent an uncharacteristically high proportion of all patients referred for prostatic surgery during this relatively short period. All this is at odds with my experience and that of my colleagues: I work in a 590 bed teaching hospital. In the 12 months to March 1989, 328 transurethral resections of the prostate were performed by the urology unit. None of the patients died, and only one patient with severe ischaemic heart disease was advised that he was unfit for surgery.

Transurethral resection performed by a trained urologist with a low mortality rate should be considered unfit for mortality has been compared to that in studies. In 1962 Holgergren² mortality in 2015 patients was myocardial infarction. His colleagues quote a low selected high risk group light the need for alternative. Their reference uses data and 1971 and reports a rising to 6-4% in autumn 80.

Since these data were have passed, during a considerable improvement. Meibohm *et al* reported³ evaluated 3885 patients: urethral prostatic resection from 1978 through operations were performed for 0-23% des significant pre-existing cardiac arrhythmias, infarction (12%), and in addition, the authors was not related to mortality. practice has reduced to a non-significant level transurethral prostatectomy. I commend Mr Williams their novel use of the procedure in a well staffed and well medicine has made a procedure even for a patient, and only very be needed to relieve a

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1 Williams G, Jager R. Mid urethral prostatic resection using an expandable metal mesh stent. *Br Med J* 1989;299:1549-52. (10 June.)
2 Holgergren H. Urethral prostatic resection. *Lancet* 1962;ii:1063-6.
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Isosflurane and midazolam in a care unit

SIR,—The letter of Dr. raises several points. The first was one of a problem to sedate in view of the amount of isoflurane has been used. After the preliminary isoflurane has been used in equivalent to 1.0 mg/kg of midazolam. L. Koog and others.¹ for sedating patients operations for generally has required the large cases described by Dr. forms of sedation were also a young adult. H each day, however, second patient require (estimated from the co-

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Zielhuis, G.A., Heuvelmans-Heinen, E.W., Rach, G.H., Van Den Broek, P. "Environmental risk factors for Otitis Media with Effusion in preschool children" Scand J Prim Health Care 7(1): 33-38, 1989.

SUMMARY: To ascertain risk factors for otitis media with effusion (OME), a cohort of 1439 preschool children, 2 years of age, was investigated by means of tympanometry at 3-monthly intervals until their fourth birthday. Parents were asked about potential risk factors for OME. Data were analysed in a case-control design with incident cases. Age, season, family size, siblings's [sic] history of OME, frequent swimming, duration of breast feeding and public day care appear to have a significant effect on OME, even after adjustment for nasal infection. Gender, race, birth weight and passive smoking were not related to OME incidence. With the exception of age and season, the relative risks of environmental factors for OME are always very low. It is concluded that the study of environmental risk factors for OME is necessary to increase the knowledge of the nature of this disease, but that it does not contribute much to medical care at the moment.

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Environmental Risk Factors for Otitis Media with Effusion in Preschool Children

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To ascertain risk factors for otitis media with effusion (OME), a cohort of 1439 preschool children, 2 years of age, was investigated by means of tympanometry at 3-monthly intervals until their fourth birthday. Parents were asked about potential risk factors for OME. Data were analysed in a case-control design with incident cases. Age, season, family size, siblings' history of OME, frequent swimming, duration of breast feeding and public day care appear to have a significant effect on OME, even after adjustment for nasal infection. Gender, race, birth weight and passive smoking were not related to OME incidence. With the exception of age and season, the relative risks of environmental factors for OME are always very low. It is concluded that the study of environmental risk factors for OME is necessary to increase the knowledge of the nature of this disease, but that it does not contribute much to medical care at the moment.

Key words: otitis media with effusion, secretory otitis media, epidemiology, risk factors, preschool children.

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INTRODUCTION

Otitis media with effusion (OME = secretory otitis media = glue ear) is one of the commonest diseases in childhood and is responsible for most of the hearing losses in this age group (1-3). Because of its silent nature - the disease remains unnoticed on many occasions - those who come to the attention of a general practitioner, paediatrician, ENT surgeon, or a public health officer form only the tip of the iceberg (4). OME has been studied world-wide, with respect to its epidemiology, natural course, diagnosis, sequelae, treatment, and risk factors.

Studying risk factors for OME is important for several reasons. First, it can give clues to the better understanding of the aetiology of the disease. This may indicate possibilities for (primary) prevention. Second, if screening is considered for OME, knowledge of risk factors may lead to the definition of high-risk groups, which should receive priority in

such a screening programme. And third, knowledge of risk factors may help doctors (GPs and others) to make a diagnosis. Such information might help to complete the clinical picture and lead to a valid diagnosis of OME.

A large amount has been written about risk factors for OME. The effect of upper respiratory tract (URT) infections on tubal function and middle ear status is widely documented and no object for dispute. Children with pathology of the URT, such as simple rhinitis, run an increased risk of developing OME (5-7). The prognostic value is much less clear for the other (environmental) risk factors. Studies on this topic often give contradictory results, perhaps because of methodological shortcomings, such as invalid measurements, small sample sizes, and lack of correction for interdependencies between risk factors.

In reviewing epidemiological studies that meet some basic scientific standards (i.e. tympanometry

¹ *Prim Health Care*

Scand J Prim Health Care 1989; 7

measurement of pneumatic otoscopy, sufficient sample size, no overt bias), we can list ten risk factors:

- **Age.** The prevalence of OME at birth is assumed to be zero. The occurrence starts to rise after 6 months, and reaches a maximum at about two years of age. The prevalence then decreases, with a small elevation at about five years. From the age of seven, OME is relatively rare. Exposure to respiratory infections is thought to be related to this typical age structure (8-10).
- **Gender.** Many studies (11, 12), but not all (5), have found a higher prevalence of OME in boys. Again this difference could be related to differences in genetic susceptibility to infections (13).
- **Race.** Some specific populations, such as Eskimos, Indians, gypsies, and Australian Aborigines are known to have higher prevalences of OME (14-16). This predominance can partly be explained by socio-hygienic conditions. Shurn et al (17) found that white children are three times more susceptible to persistent OME than black children. This can partly be explained by the higher level of medical observation and therefore the greater chance of detection in white children.
- **Family characteristics.** Family size is probably not a major risk factor for OME (18). There is conflicting data on the relevance of a family history of ear diseases or atopic diseases (5, 18, 19). There is no agreement about the importance of socio-economic status as a risk indicator for OME. If an effect exists, it is probably not due to malnourishment (5, 20) but to poor housing conditions and crowding (21).
- **Pregnancy and lactation.** Although many studies (22) show a relation between the way an infant is fed (breast/bottle) and respiratory illness the evidence for an effect of feeding practice on OME is scanty and conflicting (18, 23). The same is true for birth weight and prematurity as risk indicators for OME (24, 25).
- **Season and climate.** Higher incidences in cold seasons have been widely described (11, 24), but there is only scant evidence that specific climatic conditions are responsible for this seasonal variation.
- **Swimming.** Although it has been put forward as a risk factor, swimming has not proved to be an important prognostic factor (25).
- **Public day care.** A considerable amount of evidence on the frequency of OME has been pub-

lished on the effect of exposure to other children (8, 26-28). Again, this effect could be explained by respiratory infections.

Passive smoking. There is little evidence that parental smoking has an effect on the risk for OME. The literature is not consistent (24, 29).

Constitution and congenital abnormalities. Children with Down's syndrome, cleft palate, or Kartagener's syndrome are more at risk for OME compared with children without these congenital defects (15, 30).

The literature on the risk for OME in children with atopic constitution or allergy is inconclusive (5, 18, 19).

This review of the limited evidence available on risk factors for OME calls for further studies that cope with methodological fallacies. The present paper describes a large-scale epidemiological study on the prevalence of OME in preschool children, in which the various possible risk factors have been investigated.

POPULATION AND METHODS

The KNOOP project is a large-scale epidemiological study on the natural history of OME in preschool children, performed in the city of Nijmegen. All children born between 1 September 1982 and 31 August 1983 and living in Nijmegen on their second birthday were included. The group comprised 1439 children, from whose parents permission to take part in the study was sought. Tympanometry (Grason Stadler-27) was performed at three-monthly intervals, from the children's second birthday until four years of age. All measurements were carried out by trained audiological assistants at the children's home address. The tympanograms of all ears were classified into four types (modification of Jerger 1970).

type A: maximum compliance ≥ 0.2 ml at a middle ear pressure -99 to +200 dPa

type C1: maximum compliance ≥ 0.2 ml at a middle ear pressure -199 to -100 dPa

type C2: maximum compliance ≥ 0.2 ml at a middle ear pressure -399 to -200 dPa

type B: maximum compliance < 0.2 ml or at a middle ear pressure ≤ -200 dPa.

Type B indicates the presence of middle ear effusion. At each of the nine consecutive tympanometric

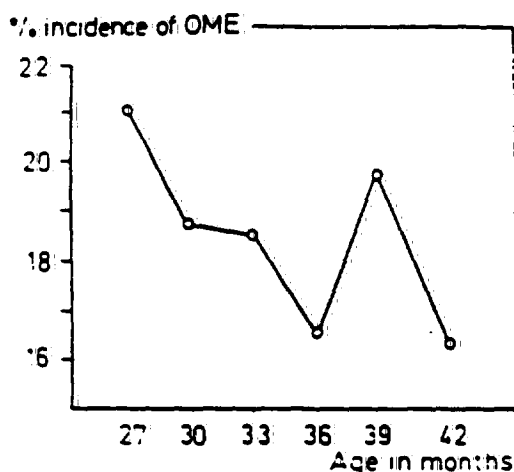


Fig. 1. Relation between age and the 3-monthly incidence of OME. Results of the KNOOP project.

screenings, the parents were asked about potentially relevant events during the three previous months, including possible risk factors for OME.

To study the effect of the factors on the risk for OME, we selected incidence data with reference to all children who did not have a type B tympanogram at a particular screening. Children in this group were considered to be patients when at least one ear showed a type B tympanogram at the next screening. The control group consisted of children with a type A tympanogram in both ears, or a combination of type A and type C1 tympanograms at this latter screening. These two groups form the basis for a case-control analysis.

Regarding family characteristics, passive smoking, type of day care, and swimming, we selected incidence data from the screening session in which the parents were asked about these factors, i.e. when the children were 27, 30, 36 and 42 months of age, respectively (sessions 2, 3, 5 and 7, respectively).

To study the effect of age, we included the data from all screening sessions until the age of 42 months. The percentage of children with at least one B tympanogram at a particular session was calculated from all children without a type B tympanogram at the former screening.

Incidence data on the other risk factors were collected at the age of 42 months. This approach is based on the assumption that risk-factor information collected at other ages will give valid estimates of the status at 42 months of age. The relative risk for all risk factors was estimated by means of an odds ratio

(OR) with a 95% confidence interval (CI). Hypotheses of elevated risk ratios were tested by means of the chi-square test. A stratified analysis was performed to take URT infections into account as a confounder, in situations where the OR was significantly above unity. Stratification was performed by dividing the study population into two groups: one group in which the children had had a serious nasal infection during the previous three months and a second which had not.

RESULTS

Figure 1 shows the relation between age and the three-monthly incidence of children with OME (= type B tympanogram). A bimodal curve with one peak at the age of 27 months and another at 39 months can be seen.

Patients and controls did not differ significantly with respect to the distribution of race, parental history of OM, breast feeding, gestation period, birth weight, and smoking by household members (Table 1). However, the following factors seem to bear a pertinent relation to the occurrence of OME.

The longer a child had been breast fed, the less the risk for OME. This trend appeared to be significant ($p < 0.05$). The risk for OME in boys was 1.4 times higher than in girls.

Family size and a history of OME in siblings were significantly related to the incidence of OME.

Season was an important factor in the aetiology of OME. With the summer as reference point, the highest risk for OME was found in winter, the smallest elevated risk in spring.

No overall association between swimming and OME could be found. Only frequent swimming, at least once a week, showed an elevated risk for OME. There was no linear trend for the frequency of swimming.

Attending public day care enhanced the occurrence of OME, but there was no linear trend in the effect of time spent at public day care.

Ten children in this study population suffered from congenital pathology of very diverse origins, and its role in the aetiology could not therefore be established.

Nasal infection appeared to be a confounder of all the significant risk factors mentioned above. After adjustment for nasal infection, all other risk factors remained (see Table 1). The confounder effect was strongest for public day care.

Table 1. Risk factors for OME, with and without correction for upper respiratory tract infections.

Environmental risk factors	No. of cases	No. of contr.	OR	p	OR*	p*
gender (m/f)	117	386	1.50	0.055	-	-
race (European/not European)	116	368	1.75	0.219	-	-
family size (1, 2, ≥ 3 children)	140	354	-	0.010	-	0.002
parental history OME (y/n)	140	354	0.80	0.303	-	-
siblings history OME (y/n)	140	354	1.85	0.005	1.66	0.024
breast feeding (n/y)	115	366	0.71	0.187	-	-
duration of breast feeding (1-4 wks/2-3 m/4-6 m/ ≥ 7 m)	86	250	-	0.176	-	-
2-3 months/1-4 weeks	35	136	1.07	0.865	-	-
4-6 months/1-4 weeks	37	110	0.64	0.234	-	-
≥ 7 months/1-4 weeks	46	124	0.57	0.113	-	-
gestation period: (≥ 38 weeks/<38 weeks)	117	386	0.74	0.354	-	-
birth weight (≤ 2500 gr/>2500 grams)	114	382	1.61	0.190	-	-
season						
autumn/winter/spring/summer	117	386	-	0.000	-	0.007
spring/summer	42	208	2.35	0.012	1.61	0.184
autumn/summer	47	215	2.59	0.004	2.19	0.019
winter/summer	60	209	3.93	0.000	2.84	0.002
swimming (last 3 months) (no/1-3x/4-11x/ ≥ 12 x)						
no/1-3x/4-11x/ ≥ 12 x	117	345	-	0.068	-	-
≥ 1 x/no	117	345	1.14	0.552	-	-
1-3x/no	82	248	1.14	0.640	-	-
4-11x/no	72	245	0.70	0.275	-	-
≥ 12 x/no	79	216	1.94	0.034	2.38	0.009
public day care (y/n)	122	337	1.88	0.007	1.71	0.023
no. of half days a week (1-2/3-4/ ≥ 5)	122	393	-	0.003	-	0.348
3-4/1-2	80	188	1.11	0.711	-	-
≥ 5 /1-2	89	320	0.50	0.004	0.73	0.207
smoking by household members (y/n)	128	307	1.11	0.643	-	-
no. of cigarettes per day (1/1-7/8-17/18-27/ ≥ 28)	127	304	-	0.274	-	-
8-17/1-7	44	76	1.24	0.599	-	-
18-27/1-7	32	89	0.60	0.236	-	-
≥ 28 /1-7	30	71	0.76	0.527	-	-

* Corrected for nasal infection by means of the method of Mantel and Haenszel in case the crude odds ratio was significantly ($p < 0.05$) above unity.

DISCUSSION

Of all the environmental risk factors studied, only a few appeared to have a significant effect on OME: age, season, family size, sibling's history of OM, frequent swimming, and public day care.

The literature also suggests a bimodal curve for

the prevalence of OME according to age (10), but in the curve we found (using incidence data) the second peak occurred at an earlier age. This indicates a faster rate of normalization of OME at about the age of 39 months. The development of the Eustachian tube and the level of maturity of the immune system may explain this.

Our finding that the highest rates of OME occurred during winter, and the lowest during the summer is in agreement with previous studies (9, 11). After adjustment for common colds, there was still a significant relationship between season and OME, but only for autumn and winter seasons. In the context of the KNOOP-project, the connection between OME and weather conditions has been studied (31). Low temperatures and few hours of sunlight appeared to be relevant factors.

According to the literature, the family history of OME (parents or siblings) is predictive for the occurrence of OME. Our data, however, showed only a significant relation with family size and history of OM in siblings. Our implication of the type of day care in the aetiology of OME agrees with other authors (8, 26-28). However, the trend in our study for the more time children are exposed to other children, the more they develop OME, was not significant. All these results seem to indicate that OME is a contagious disease.

It was shown by Ishidoya et al (25), as in our project, that swimming was not an important risk factor. Only frequent swimming, at least once a week, showed some effect in our data. More studies, which consider the swimming environment and the type of swimming water as well, are necessary to establish the specific effect of swimming behaviour.

In spite of our criticism of other studies in the introduction, we did not perform multivariate analyses. But, due to the design of the study, age and season are uniformly distributed among the other factors. The other risk factors we found to be significant are independent of each other on account of their nature.

It is generally accepted that URT infections play an important role in the pathogenesis of OME and therefore are a potential confounder in risk factor analyses. Surprisingly, we found that the effect of risk factors on the incidence of OME remained significant after correction for URT infections. However, it should be noted that we adjusted for nasal infection in the preceding three months, before a case of OME was diagnosed. This may have caused some misclassification and thereby incorrect confounder control.

That we could not find a significant effect for the remaining risk factors does not necessarily mean that they have no effect on OME. Further in-depth studies, in which a direct relationship between nasal infections and OME must be taken into account, are

necessary to clarify the effect of these factors on OME.

It should be noted that the relative risks of environmental risk factors, with the exception of age and season, were always very low, though sometimes significant. This has relevance in the context of preventive and clinical practice.

- With such low relative risks, it is impossible to reduce the OME incidence substantially by means of (primary) prevention. Moreover, these factors do not lend themselves to intervention strategies.
- If a screening program for OME is considered, it should be realized that the risk factors found do not lead to a clear definition of high-risk groups, i.e. groups that contain most of the OME cases.
- In the context of OME diagnosis, knowledge of risk factors has a low predictive value. The only environmental factors strong enough to justify inclusion in medical decisions are age and season.

This means that studying environmental risk factors for OME is mainly a scientific activity that could help to increase our knowledge of the nature of the disease, without making a significant contribution to medical care at the moment.

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Pukander, J., Sipila, M., Kataja, M., Karma, P. "Estimating the Risk of Acute Otitis Media Among Urban Children" Ann Otol Rhinol Laryngol Supplement 99(149): 18-20, 1990.

The present study comprised a cohort of 1,294 children followed from the age of 7 months to the age of 2 years. Epidemiologic data were collected during the children's regular checkup visits at child health-care centers, and their ears were examined and, if necessary, treated in specific study clinics. The "overwhelmingly highest risk indicator" was day-care outside of the home. The results of this study suggest that a mother's smoking may increase most the risk to the baby of contracting acute otitis media and especially of recurrent attacks of otitis media. The authors conclude that "the best place for a small child during the first years of life is in his own house where the mother breast-feeds him and does not smoke."

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TABLE 7. AGE AT FIRST EPISODE OF AOM IN RELATION TO NUMBER OF EPISODES OF AOM PER CHILD

No. of Episodes per Child	Age at First Episode							
	<1 yr		1 yr		>2 yr		Total	
	No.	%	No.	%	No.	%	No.	%
1	295	28	407	41	650	69.0	1,352	45
2-3	430	41	411	42	257	27.5	1,098	37
4-5	200	19	128	13	30	3.0	358	12
6-16	130	12	35	4	5	0.5	170	6
Total	1,055	100	981	100	942	100.0	2,978	100

AOM — acute otitis media.

AOM — acute otitis media.

among children born in 1977 and living in different districts and different types of houses in the city of Malmö was studied in three different districts (center of the city, Rosengård, and Oxie). In the center of the city most families live in older, mainly well-maintained apartment houses. Rosengård is a modern crowded tenement house district built in the 1960s and 1970s. Oxie is a modern crowded villa suburb outside Malmö built in the later 1970s. The children living in Oxie had the highest cumulative incidence rate. At the end of the observation period of 5 years, about 65% of the children had had at least one episode of acute otitis media with effusion. The corresponding figures for the children living in Rosengård and in the center of the city were about 55% and 45%, respectively. The differences among the districts were significant ($p < .001$).

In order to study the importance of day-care type and the importance of age at first episode to the total number of episodes per child, 2,978 children were followed during their first 4 years of life. The children were born from 1977 to 1979 and had been registered for at least one episode of acute otitis media. Among children attending public day-care centers for the first time before the age of 2 years, 8% were registered for six or more episodes of acute otitis media during their first 4 years of life. In children attending public day-care centers for the first time between the ages of 2 and 3 years, 5% had six or more episodes of acute otitis media during the corresponding time. For children cared for at home or privately during their first 4 years of life, 3% were registered for six or more episodes of acute otitis media. The difference between the groups was statistically significant ($p < .001$).

Table 7 shows the age at the first episode of acute otitis media in relation to the total number of episodes per child during the first 4 years of life. Forty-five percent of the children had only one episode, while 6% were registered for six or more episodes. Among 1,055 children having their first episode of acute otitis media before the age of 1 year, 12% were registered for six or more episodes. The

corresponding figure among 942 children having their first episode after the age of 2 years was 0.5%. The difference between the groups was significant ($p < .001$).

The study of the medical records of 504 children from the otolaryngology and pediatric departments showed that the otitis-prone children were registered for a mean number of 39 ambulatory visits per child during their first 4 years of life, as compared to 9 visits per child in the control group.

In the otitis-prone group myringotomy was performed at least once in 67% of the children. Fifty-two percent had tympanostomy tubes inserted and 19% had undergone adenoidectomy. The corresponding figures from the control group were myringotomy, 13%; tympanostomy tubes, 6%; and adenoidectomy, 6%.

The occurrence of other diseases diagnosed in the children showed that in the otitis-prone group, 53% had been found to have bronchopulmonary diseases at least once, 44% had been treated for gastrointestinal diseases, and 36% had been found to have allergic symptoms or diseases at least once. The corresponding figures for the control group were bronchopulmonary diseases, 32%; gastrointestinal diseases, 33%; and allergic symptoms or diseases, 17%. The difference between the two groups was statistically significant ($p < .001$).

CONCLUSIONS

The incidence rate of acute otitis media was highest in 1-year-old boys. At the age of 3 years, about 50% of all children in Malmö had had at least one diagnosed episode of acute otitis media. At the age of 7 years, the corresponding figures were 65% to 70%.

The incidence of acute otitis media was found to vary among children living in different districts and in different types of housing in the city. Children attending public day-care centers early in life were more prone to recurrent episodes of acute otitis media than those attending public day-care at later ages, or those children cared for at home or in private care.

Children having their first episode of acute otitis media before the age of 1 year run a greater risk of being otitis-prone than those having their first episode after the age of 1 year. Children with recurrent episodes of acute otitis media early in life also seem to be more prone than other children to other kinds of diseases, i.e., bronchopulmonary, gastrointestinal, and allergic diseases.

It is important to detect and recognize otitis-prone children as early as possible in order to be able to offer them treatment and long-range control.

ESTIMATING THE RISK OF ACUTE OTITIS MEDIA AMONG URBAN CHILDREN

JUHANI PUKANDER, MD; MARKKU SIPILÄ, MD; MATTI KATAJA, PHD; PEKKA KARMA, MD

Acute otitis media is an increasingly important health problem among the pediatric population. Only a few children escape acute otitis media during their childhood days.¹ Many factors may affect the liability of a small child to contract acute otitis media. These factors are un-

dergoing continuous change along with changes in the way of living and behavior of the entire society. One of the most prevalent changes is the arrangement of day-care for children, because increasingly both parents are working outside the home.²

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TABLE 8. STEPWISE MULTIVARIANT ANALYSIS OF INTERRELATED POWER FUNCTION OF VARIABLES AFFECTING OCCURRENCE OF AOM AMONG 1,294 CHILDREN

	Rank of Importance Along With Minimum No. of AOM Attacks per Child					Correlation Coefficient (r) of Separate Variables Affecting Occurrence	
	1	2	3	4	5	Children With at Least 1 AOM Attack (no/yes)	Total No. of AOM Attacks per Child
Attending day-care center	1	1	1	1	1	0.161*	0.263*
Sibling(s) with AOM attacks during follow-up	4	2	2	2	2	0.129*	0.142*
Attending family day-care	8	4	5	3	9	0.088†	-0.009
Type of housing	3	6	9	9	7		
Smoking of parent(s)		8	6	4	4		
Mother's respiratory infections before follow-up	5	3	11	11		0.062	0.023
Birth weight	15	11	3	10	10	0.032	-0.009
Father's respiratory infections before follow-up	11	7	8			0.009	-0.003
Nighttime bottle in supine position			10	6	6	-0.028	-0.001
Floor area per person at home			13	5	3	-0.008	-0.056
Viral respiratory infections and tonsillitis of sibling(s) during follow-up	2	9			5	0.123*	0.079†
Socioeconomic status	7		7			-0.030	-0.050
Pets	13			8		-0.093§	-0.023
Allergy of parent(s)	14			12		-0.015	0.004
Breast-feeding		13	4			0.024	-0.015
Indoor humidification	9	10	12			0.068§	0.067§
Sex (boys had more AOM attacks)	10	12				0.015	0.076†
Allergy of child	12	5				0.061†	0.062
Respiratory infections of parent(s) during follow-up	6				8	0.093§	0.053
Place of residence				7			
No. of siblings						0.063†	0.090§
Positive otitis history of parent(s)						0.101§	0.097§

AOM — acute otitis media.

*p < .001.

†p < .05.

§p < .01.

In addition to human suffering, recurrent otitis attacks with effusion inside the middle ear impair the child's hearing ability at an age that is critical for the acquisition of linguistic skills. Children who have had prolonged middle ear effusion have shown depressed scores on intelligence tests, impaired development of speech and language, and poor performance in school.⁴⁴ The preventive procedures for this common and harmful illness are by no means composed only of medical aspects. Social and health educational factors play a very important role, too. That is why we are trying to analyze the combined risk of acute otitis media with a multivariant forecasting model.

The present analysis comprised a cohort of 1,294 children followed from the age of 7 months to the age of 2 years. Relevant epidemiologic data were collected during their regular checkup visits at child health-care centers, and their ears were examined and disorders were treated in specific study clinics.

A forecasting model for calculating the interrelative importance of given risk indicators was developed.⁴⁵ This mathematic method, i.e., to find the best forecasting model in the Bayesian sense, follows the idea of stepwise multiple regression analysis, searches through all variables listed, and selects one by one the variable improving the model most, or at least affecting it with the fewest drawbacks if not improving it. The worth of the model is measured by

the sum of false negatives and false positives. The minimum of this sum builds the optimum of the model. The variables in this list above this optimum affect the risk, with the rest of the variables being no longer useful in this forecasting model. In other words, the Bayesian approach reveals the variables containing any noticeable influence on the occurrence of acute otitis media. In our hands this model gave a correct classification in 65% to 71% of the cases; the higher the percentage, the higher the number of recurrent attacks per child.

Of the 22 variables studied, 12 to 15 were found to affect the combined risk of contracting one or more attacks of acute otitis media. The rank of importance of these 22 variables is shown in Table 8, indicating the interrelated power function of different variables in contracting acute otitis media.

The overwhelmingly highest risk indicator was day-care outside the study child's own home, regardless of how many recurrent attacks of acute otitis media were included in the analyses. However, this risk indicator became more important along with the increased number of recurrent attacks. Acute otitis media currently is preceded very often by upper respiratory tract infections,⁴⁶ and such infections tend to spread more easily the higher the population density. Day-care nurseries create a favorable environment for respiratory viruses to spread,⁴⁷ with acute

otitis media as a sequela. Next in the risk indicator list came the number of attacks of acute otitis media among siblings, most probably because of increased exposure of a baby to infections brought in from outside the home; this was especially true with recurrent attacks. The same phenomenon can be seen with the type of housing, also.²² The bigger the house with very many families living there, i.e., apartment buildings, the higher the concentration of virus particles in the air inhaled by a baby.

Passive smoking is quite newly observed as a risk factor for acute otitis media, although there are contradictory reports on this point.^{21,23} Our results showed that the mother's smoking seemed to increase most the risk to the baby of contracting acute otitis media and especially of contracting recurrent attacks. The number of smoking mothers in Finland is fortunately low, but on the other

hand, because of this, information is sparse, and very definitive conclusions could not be drawn in this study. The protective effect of prolonged breast-feeding against respiratory infections is well known,²⁴ whereas data on its protective effect against acute otitis media are, however, now accumulating.²⁵ Our patients seemed to enjoy some protection against acute otitis media, but only during the first 12 months of life, i.e., during breast-feeding time. Breast-feeding babies is becoming more fashionable again after a period of underrating this natural way of nourishment,²⁶ so future studies will reveal the optimal length of this "therapy."

In conclusion, this study suggests that the best place for a small child during the first years of life is in his own house where the mother breast-feeds him and does not smoke.

CURRENT STATUS OF OTITIS MEDIA IN THE AMERICAN INDIAN POPULATION

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The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service, US Public Health Service.

Incidence and prevalence determinations for a given disease typically involve specific research designs for those purposes. In the Indian Health Service (IHS), where resources for research are lacking, it is usually necessary to make prevalence estimates inferentially from assessing hospital records. The data in this report are based upon the number of visits for acute and chronic otitis media, with individual patients unspecified, and analyses of actual patient counts.

Otitis media was first listed in the IHS as a reportable disease in 1962. It has been no lower than the second highest in annually reported visits since that time, even though a special program was begun in 1970 to provide for the remediation and control of otitis media in American Indian and Alaska Native communities throughout the United States.

Over the 15 years of the otitis media program's existence (Table 9), hospital visits for acute and chronic otitis media have increased by 44%. During the same time the patient population has increased by 49%. The ratio of first visits to revisits changed over the first 10 years. For acute otitis media, the first visit to revisit ratio has changed from 62% to 54% for the first visit only. For chronic otitis media, the ratio has been more constant, from 32% to 38% for the first visit only. These data indicate increased awareness for follow-up for acute otitis media and less concern for follow-up for chronic otitis media. These findings, and all others not otherwise referenced, are from internal reports compiled by the IHS (Table 9).

An observation of particular interest in Table 9 is the consistency in the number of diagnoses of acute versus chronic otitis media in spite of the absence of IHS-wide criteria for defining acute and chronic disease. In general, the diagnosis of the physician is tabulated as recorded. In his assessment of patient care records, Toubbeh²⁷ found that in Alaska, Montana, and southern Arizona there was a high consistency in the diagnoses of chronic disease based upon presence of perforation, duration of the episode, and

time between episodes. In Alaska, where 26.9% of the diagnoses were termed chronic otitis media, 1.1% showed perforation; in Montana, 9.5% cases were diagnosed chronic, with 0.8% showing perforation; in southern Arizona, 10.1% were diagnosed chronic, with 0.4% showing perforation. The consistency in diagnoses over time in Table 9 is noteworthy considering the IHS physician turnover rate and the wide variety of medical backgrounds of those making the diagnoses.

Evaluation of hospital records over the years of the program's existence shows three variables — sex, age, and blood quantum — to be particularly significant in making inferences about the natural history of otitis media.

TABLE 9. NUMBER OF OUTPATIENT VISITS FOR ACUTE AND CHRONIC OTITIS MEDIA, FISCAL YEARS 1971 TO 1985

Fiscal Year	Acute Otitis Media		Chronic Otitis Media		Total
	No. of Visits	%	No. of Visits	%	
1985	135,941	72.7	51,126	27.3	187,067
1984	129,022	71.7	50,731	28.3	179,753
1983	120,330	70.7	49,851	29.3	170,181
1982	108,561	69.8	47,029	30.2	155,590
1981	97,415	65.6	51,121	34.4	148,536
1980	90,408	70.0	38,668	30.0	129,076
1979	87,965	71.2	35,539	28.8	123,504
1978	95,692	81.5	21,671	18.5	117,363
1977	83,787	80.2	20,651	19.8	104,438
1976	81,128	79.5	20,941	20.5	102,069
1975	76,889	77.5	22,304	22.5	99,193
1974	74,915	78.3	20,717	21.7	95,632
1973	80,508	79.0	21,382	21.0	101,890
1972	74,107	77.7	21,312	23.3	95,419
1971	60,486	73.6	21,723	26.4	82,209

From Program Statistics Branch, Indian Health Service, Public Health Service, Department of Health and Human Services, Rockville, Md.

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ABSTRACT. The distribution of tympanogram types among 872 seven-year-old children from a random population sample was related to 14 features of the home environment reported by parents in a questionnaire. Parental smoking was an important determinant of middle ear underpressure and effusion, and accounted for much of the associations observed with dampness, crowding and rented accommodation. Gas cooking was associated with a higher prevalence of effusion, but a lower prevalence of underpressure: this may deserve further study.

After adjustment for seasonal variation, tenure and household smokers, the weekly mean temperature in the bedrooms of 34 children with Type B tympanograms was 18.2°C compared to 17.9°C for 190 children with Type A tympanograms. The equivalent figures for bedroom relative humidity were 51.8 per cent and 52.7 per cent. It is unlikely that heating or ventilation of the home is an important determinant of middle ear effusion and underpressure in this age-group.

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Impedance tympanometry and the home environment in seven-year-old children

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Abstract

The distribution of tympanogram types among 872 seven-year-old children from a random population sample was related to 14 features of the home environment reported by parents in a questionnaire. Parental smoking was an important determinant of middle ear underpressure and effusion, and accounted for much of the associations observed with dampness, crowding and rented accommodation. Gas cooking was associated with a higher prevalence of effusion, but a lower prevalence of underpressure; this may deserve further study.

After adjustment for seasonal variation, tenure and household smokers, the weekly mean temperature in the bedrooms of 34 children with Type B tympanograms was 18.2°C, compared to 17.9°C for 190 children with Type A tympanograms. The equivalent figures for bedroom relative humidity were 51.8 per cent and 52.7 per cent. It is unlikely that heating or ventilation of the home is an important determinant of middle ear effusion and underpressure in this age-group.

Introduction

Little is known about the aetiology of middle ear effusion (Black 1985a), although evidence is accumulating of a substantial risk from passive exposure to tobacco smoke (Kraemer *et al.*, 1983; Black, 1985b; Hinton and Buckley, 1988; Strachan *et al.*, 1989). Studies in pre-school children have reported upon the relationship between middle ear disease and conditions in day care centres (Iversen *et al.*, 1985) and in the home (Birch and Elbrond, 1987), but no similar information has been published for children of school age. Although the overall prevalence of middle ear effusion is lower in older children, persistent effusions present a considerable burden to hospital services, and rates of surgery for glue ear are greatest in the five-seven year age group (Black, 1984).

The relationship between indoor air quality and respiratory disease in children has been extensively investigated using symptoms and ventilatory function as outcome variables. Particular areas of concern are possible hazards from suspended particulates due to parental smoking or household fires, nitrogen dioxide derived from unvented gas or paraffin appliances, and aero-allergens, such as mould spores or faeces of house dust mites, both of which tend to be more prevalent in damp houses (Samet *et al.*, 1987, 1988).

Tympanometric abnormalities are highly sensitive to frequent or persistent upper respiratory infections (Tos *et al.* 1979), and may therefore be a useful indicator of more general respiratory effects due to indoor air pollution. This paper explores the relationship between tympanometric findings and the home environment among seven-year-old children participating in a survey

of the effect of damp housing upon respiratory disease (Strachan, 1988; Strachan and Sanders, 1989).

Methods

Sample selection

All children in their third (P3) year at a random sample of one in three primary schools within the Edinburgh city boundary were chosen. These children were aged 6½ to 7½ years in September 1986.

In the last week of November 1986, a postal questionnaire was sent to their parents, enquiring about respiratory symptoms in the child and conditions in the home, and including a form of consent to the remainder of the study. Children absent at the time of the launch were given a questionnaire on their return, and parents who had not responded after ten days were contacted by letter or telephone to maximize the number of replies. The parents of 1095 children received a questionnaire and usable replies were obtained from 1012 (92 per cent).

Written consent to further tests was obtained for 941 children (86 per cent of the target sample). Twenty of these children left school before examination, and two of the smallest schools (accounting for a further 20 children) were used for pilot studies of the respiratory examination protocol. The number of children eligible for inclusion in the clinical survey was therefore 901 (82 per cent of the target sample), 892 (99 per cent) of whom were eventually examined.

Ethical approval was obtained from the Paediatric/Reproductive Medicine Ethics of Medical Research Sub-Committee of the Lothian Health Board and from the Research Committee of the Department of Education, Lothian Regional Council.

Impedance tympanometry

Children were tested at school by the author during the period January to June 1987. Middle ear pressure, compliance, and the relative gradient of the tympanometric curve were measured on both ears using a MicroLab 'Earscan' configured for impedance measurements (Micro Audiometrics, Port Orange, Florida, USA). This uses a probe tone of 226 Hz at 85 dB and sweeps from +200 to -312 daPa at 100 daPa/sec. Subjects were asked to swallow a sip of water immediately prior to the measurement, to ensure that patent eustachian tubes would be ventilated. Tympanogram types were defined on the basis of the modified Jerger classification proposed and validated by Fiellau-Nikolasen (1983):

Type	MEP (daPa)	Gradient	Interpretation
A	+200 to -99.9	>10%	Normal tympanogram
C1	-100 to -199.9	>10%	Mild underpressure
C2	-200 to -312	>10%	Severe underpressure
B	No peak	<10%	Middle ear effusion

The tympanogram type from the more abnormal ear of each child was used in the analysis. This permitted the inclusion of 23 children with satisfactory results from only one ear.

Monitoring of bedroom temperature and relative humidity

During the period January to April 1987, an attempt was made to visit the homes of 377 children, comprising all those in eight schools, those in the top quintile of the estimated bedroom humidity distribution (as described in detail by Strachan and Sanders, 1989) and the remainder of the homes reported to be affected by dampness or mould growth.

In each home, the temperature and relative humidity of the child's bedroom were monitored for seven days by thermohygrograph (Casella Ltd, London, UK). This instrument measures temperature by bimetallic strip and humidity by changes in the length of a treated human hair, and both are charted on a slowly moving drum. The thermohygrographs were installed in a position between three and six feet high and out of direct sunlight. On completion of the recording, their calibration was checked by a spot measurement of wet and dry bulb temperature using an aspirated psychrometer. The relative humidity was calculated from the wet and dry bulb thermometer readings using standard formulae (British Standards Institution, 1965).

Thermohygrograph charts were digitized for computer analysis and mean weekly values for temperature and relative humidity were calculated. Measurements were taken in 330 homes, of which 307 were usable in this analysis (81 per cent of the target sample). Technical problems with the instruments, including interference by the child or their siblings, accounted for most of the unusable recordings.

Relative humidity is a function of both vapour pressure (which reflects absolute humidity) and temperature (which determines the saturation vapour pressure at which condensation will occur). The relationship between indoor relative humidity and outdoor conditions is complex, depending upon the respective temper-

atures and vapour pressures. Thus, in well-heated bedrooms relative humidity was lower in colder weather, reflecting the lower outdoor vapour pressure usually found during the winter. However, in poorly-heated bedrooms the relative humidity was higher during the winter, because it was determined by the indoor temperature which varied to a greater extent with external conditions. Weekly mean indoor temperature and relative humidity measurements were adjusted for external climatic variations, as described in detail elsewhere (Strachan and Sanders, 1989).

Statistical analysis

Preliminary analyses were performed using Statistical Analysis System (SAS Institute Inc, 1985). The effect of housing conditions upon the distribution of tympanogram types was determined for 14 characteristics of the home environment reported in the questionnaire: tenure, number of persons per room, number of smokers in the household, use of gas for cooking, use of a coal fire, bottled gas appliance, paraffin heater, wood stove, presence of damp patches on walls, patches of mould or fungus, and the following characteristics of the child's bedroom during the winter months: number of children sleeping in the room, heat at night, heat during the day, and window left open at night. Most of the findings were negative, and results are presented in full only for seven variables for which an aetiological role in upper respiratory disease has been suggested by other studies. Trends in prevalence of Type B tympanograms across 2 × k contingency tables were assessed by the χ^2 statistic proposed by Mantel (1963).

The effect of housing conditions was investigated further by multiple logistic regression analysis, using the GLIM statistical package (Baker and Nelder, 1978). Middle ear effusion (Type B tympanogram) was treated as the outcome variable, and those with Type A or Type C tympanograms as the comparison group. Housing tenure, domestic crowding (more than one person per room), gas cooking and dampness were treated as dichotomous explanatory variables, and the number of smokers in the household was included as a factor with three levels: none, one, two or more.

Results

Tympanometric data for the more abnormal ear of 872 children (98 per cent of those tested) were available for analysis. Overall, there were 546 Type A, 149 Type C1, 95 Type C2 and 82 Type B tympanograms. Twenty-six of the 82 children with a flat tympanogram in one ear had a flat tympanogram in the other.

Table 1 shows the distribution of tympanogram type by housing conditions, as reported in the postal questionnaire. Missing questionnaire data slightly reduced the numbers available for analysis by each housing variable. Middle ear pressure was lower among children from rented or crowded homes and from families with two or more smokers. Domestic fuels, dampness and mould growth had small or inconsistent effects upon the prevalence of underpressure (Types B and C combined), although Type B tympanograms were more common in all the 'exposed' categories.

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TABLE I
Prevalence (%) of middle ear effusion and underpressure in the more abnormal ear by reported housing conditions

		More negative middle ear pressure (daPa)			
		+100 to -100 (Type A)	-200 to -100 (Type C1)	-300 to -200 (Type C2)	Negative no peak (Type B)
Tenure	own	64.6 (396)	16.3 (100)	10.6 (65)	8.5 (52)
	rent	57.8 (147)	18.5 (47)	11.8 (30)	11.8 (30)
Persons per room	<1.0	64.2 (187)	15.5 (45)	12.7 (37)	7.6 (22)
	1-1.5	62.0 (268)	19.0 (82)	8.6 (37)	10.4 (45)
	1.5+	59.8 (65)	13.9 (15)	14.8 (16)	11.1 (12)
Smokers in household	0	63.9 (292)	17.3 (79)	10.7 (49)	8.1 (37)
	1	63.3 (169)	16.5 (44)	10.9 (29)	9.4 (25)
	2+	56.4 (79)	17.1 (24)	12.1 (17)	14.3 (20)
Gas cooker	no	60.5 (221)	21.1 (77)	11.0 (40)	7.4 (27)
	yes	64.1 (320)	14.2 (71)	10.6 (53)	11.0 (55)
Coal fire	no	63.1 (511)	16.9 (137)	10.6 (86)	9.4 (76)
	yes	59.3 (32)	16.7 (9)	13.0 (7)	11.1 (6)
Dampness on walls	no	62.9 (462)	17.7 (130)	10.8 (79)	8.6 (63)
	yes	60.0 (78)	13.8 (18)	12.3 (16)	13.8 (18)
Mould growth	no	62.7 (492)	17.4 (137)	11.0 (86)	8.9 (70)
	yes	62.0 (49)	13.9 (11)	11.4 (9)	12.7 (10)

Number of children in parentheses.

The most marked difference in the prevalence of Type B tympanograms was between homes without smokers and those in which two or more adults smoked cigarettes. Overall, the trend of increasing prevalence with increasing number of smokers in the household was significant ($\chi^2 = 4.15$, $df=1$, $p<0.05$). The difference between owned and rented homes ($\chi^2 = 1.95$, $df=1$, $p>0.10$) and the trend of increasing prevalence of flat tympanograms with increasing housing density ($\chi^2 = 1.77$, $df=1$, $p>0.10$) could readily have occurred by chance. The prevalence of effusion was somewhat greater in the homes with damp patches on the walls ($\chi^2 = 3.01$, $df=1$, $0.05<p<0.10$).

There was also an excess of effusions in the homes with gas cooking ($\chi^2 = 2.81$, $0.05<p<0.10$), although the prevalence of underpressure was lower in this group. The number of children exposed to other sources of nitrogen dioxide in the home was small, but in each group the prevalence of Type B tympanograms was higher than among unexposed children: 11.3 per cent (7/62) for those exposed to bottled gas stoves, and 18.2 per cent (4/22) for children in homes with paraffin heaters.

In contrast to the effect of passive smoke exposure on the prevalence of middle ear effusion, the prevalence of pain or discharge in the ear over the past year differed little between non-smoking homes (23.5 per cent), homes with one smoker (25.3 per cent) and homes with two or more smokers (24.4 per cent). The corresponding proportions of children reported to have had tonsils or adenoids removed were 11.6, 14 and 12.1 per cent respectively. The prevalences of recent ear trouble and tonsillectomy or adenoidectomy varied little with respect to housing tenure, the use of gas for cooking, or the presence of dampness in the home (Strachan, 1988).

The prevalence of parental smoking (particularly both parents smoking) was higher in rented or crowded homes, and in homes affected by dampness or mould growth. When adjusted by multiple logistic regression for the effects of housing tenure, domestic crowding, gas cooking and damp walls, the excess of Type B tympanograms among children from homes with one smoker

in the household (compared to none) was negligible (odds ratio 1.04, 95 per cent confidence interval 0.56-1.78). The effect of two or more smokers remained substantial, although of borderline significance when compared to non-smoking households (odds ratio 1.80, 95 per cent CI 0.96-3.40). The odds ratio estimates for Type B tympanograms, independent of parental smoking and other factors, were 1.28 (0.73-2.21) for rented housing, 1.05 (0.70-1.57) for domestic crowding (more than one person per room) and 1.38 (0.73-2.59) for damp patches on walls. The association of gas cooking with middle ear effusion was not confounded to any great extent by these factors, the adjusted odds ratio for homes with gas cooking being 1.40 (0.90-2.18).

The effect of indoor air quality was explored in more detail among the 307 children with tympanometric data whose homes had been visited in the thermohygrograph survey. Table II shows the mean temperature and relative humidity, adjusted for climatic variation, in groups defined by tympanogram type. There was little overall heterogeneity, and no evidence of a significant trend in bedroom temperature or humidity with degree of tympanometric abnormality. Further adjustment for housing tenure and the number of smokers in the household made little difference to these results (Table II). The mean temperature or relative humidity in each group might be misleading if the relationship between indoor conditions and middle ear disease were U-shaped, rather than linear. However, inspection of the spread of readings within each tympanogram group did not suggest that tympanometric abnormalities were more or less common at each extreme of the temperature or relative humidity distributions.

Discussion

This study has confirmed the importance of parental smoking as a risk factor for middle ear effusion, as discussed in detail elsewhere (Strachan *et al.*, 1989). Of the remaining factors studied, gas cooking emerged as the

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TABLE II
Mean adjusted weekly mean bedroom temperature and relative humidity by tympanogram type

	Tympanogram types				F statistics*	
	A	C1	C2	B	ANOVA	trend
<i>As measured:</i>						
Temperature (°C)	17.87	17.27	17.72	18.18	2.09	0.07
Relative humidity (%)	52.70	54.99	51.93	51.99	2.18	0.23
<i>Adjusted for tenure and number of smokers:</i>						
Temperature (°C)	17.88	17.32	17.76	18.19	1.95	0.20
Relative humidity (%)	52.73	54.95	51.90	51.84	2.19	0.25
Number of children	190	59	33	34		

*Tests for heterogeneity (ANOVA) have 3 and 303 df. All are $p > 0.05$.

Tests for trend have 1 and 305 df. All are $p > 0.10$.

with the strongest independent relationship to middle ear effusion, although it was quite likely that this association could have occurred by chance. The excess of middle ear effusions among children with unvented gas or paraffin appliances in the home was consistent with a hazard due to nitrogen dioxide exposure, although the overall prevalence of middle ear under-pressure was lower in the children from homes with gas cookers. Such a discrepancy suggests chance variation rather than a causal relationship. This is the first report upon the association between gas cooking and middle ear disease, but Black (1985b) described a significant excess of cases attending for glue ear surgery among children from homes with open gas fires or paraffin heaters, which was attributable to confounding by parental smoking and birthplace. The present results should be regarded as a stimulus to further studies, rather than conclusive evidence for or against an environmental health hazard. Such studies may need to be large, or to use direct measures of pollutant levels, since a simple dichotomy between gas and other cooking fuel is a relatively crude indicator of personal nitrogen dioxide exposure (Ogston *et al.*, 1985).

These results do not suggest that the temperature or humidity of the home environment is an important determinant of middle ear effusion in children of primary school age. However, because the study was based upon children attending school, the proportion of their time spent in the home was less than for younger children. Caution is required in extrapolating these conclusions to other age-groups. Birch and Elbrond (1987) found that both minimal and copious ventilation through windows were associated with fewer Type B tympanograms in children aged 0-6 years but no direct measurements of indoor air conditions were obtained.

These findings were based upon small numbers in each group and are difficult to interpret because copious ventilation was often associated with heavy smoking in the home.

Both high and low ambient relative humidity have been proposed as factors promoting the spread of viral respiratory infections in droplet spray (Lester, 1948; Kingdom, 1960; Buckland and Tyrell, 1962). The lack of any relationship of tympanometric findings to ambient humidity in the child's bedroom does not suggest that domestic humidity is a significant factor in the transmission or infectivity of such infections. In this age-group,

however, much of the transmission by droplet spray may be expected to occur at school.

Spot measures of relative humidity at the time of examination revealed much drier conditions in schools than in children's bedrooms, with relative humidity generally below 40 per cent. A review of controlled studies of humidification in working environments by Green (1984) suggested that the incidence of upper respiratory illnesses in adults is reduced if humidity is raised above this level, perhaps because drying and cracking of the nasal mucosa reduces host resistance. It is therefore possible that indoor atmospheric conditions at school were influential in determining the prevalence of middle ear effusion in these children, despite the lack of correlation between bedroom conditions and tympanometric findings. However, Iversen *et al.* (1985) found no relationship between middle ear effusion in younger children and the temperature, relative humidity or carbon dioxide concentration in their day centre. A similar investigation among children of early primary school age would be useful. Indeed, all studies exploring the respiratory effects of indoor air quality might consider the objective and sensitive technique of impedance tympanometry for inclusion alongside more conventional disease outcomes.

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ETS AND ADULT RESPIRATORY DISEASE/SYMPTOMS

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ADULT RESPIRATORY DISEASE

Several studies have examined respiratory disease and symptoms and their possible association with exposure to environmental tobacco smoke in adults. The studies that examined respiratory disease and symptoms in adults are contained in this section. For additional studies on adults, see the "compromised individuals" and "lung function" sections.

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RESULTS OF SELECTED STUDIES: ETS AND ADULT RESPIRATORY HEALTH

Lee, 1986

Passive smoking was not associated with an increased risk of chronic bronchitis in the nonsmoker.

Koo, et al., 1988

Reported an association between respiratory symptoms in the mothers and the same symptoms in their children. Indicates that cross-infection is an important confounder of studies on parental smoking and childhood respiratory health.

Hole, et al., 1989

Reported an association between passive smoking and adverse cardiorespiratory symptoms in adult nonsmokers. None of the associations, however, were significant.

Koo, et al., 1990

With the exception of smoking by the father and the children's NO₂ levels, no association was found between smoking at home and NO₂ levels.

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Lee, P.N., Chamberlain, J., Alderson, M.R. "Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases" British Journal of Cancer 54: 97-105, 1986.

SUMMARY: In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischaemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all.

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Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases

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Summary In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischaemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all.

Study of hospital in-patients

In 1977 a large hospital case-control was initiated to study the relationship of the type of cigarette smoked to risk of lung cancer, chronic bronchitis, ischaemic heart disease and stroke. This study was carried out in 10 hospital regions in England; interviewing ended in January 1982. The original questionnaire did not include questions on passive smoking as it was not considered an important issue in 1977. However, in 1979 it was decided to extend the questionnaire to cover passive smoking for married patients for the last four regions to begin interviewing. Subsequently, in 1981, following publication of the papers by Hirayama (1981) and by Trichopoulos *et al.* (1981) claiming that non-smoking wives of smokers had a significantly greater risk of lung cancer than non-smoking wives of non-smokers, it was decided to increase the number of interviews of married lung cancer cases and controls. The extended questionnaire was then administered to these patients in all hospitals where interviewing was still continuing.

Follow-up study of spouses of non-smoking hospital in-patients

In 1982, after interviewing of hospital in-patients had been completed, it was decided to carry out a follow-up study. In this study, an attempt was

made to interview the spouses of all of the married hospital in-patients with lung cancer who reported never having smoked, as well as of two married non-smoking controls for each of these index lung cancer cases. The follow-up study was intended partly to compare information on spouses' smoking habits obtained first-hand with that obtained second-hand during the in-patient interviews, and partly to obtain some data on spouses' smoking habits for those patients who had not answered passive smoking questions in hospital.

This paper concentrates solely on the issue of passive smoking in lifelong non-smokers. Results relating to type of cigarette smoked are described elsewhere (Alderson *et al.*, 1985), while a detailed report, available on request from PNL, considers the overall findings from this case-control study.

Methods and response

Study of hospital in-patients

For each of the 4 index diagnoses (lung cancer, chronic bronchitis, ischaemic heart disease and stroke), the intention was to interview 200 cases and 200 matched controls in each of the eight sex/age cells (i.e. male or female, and aged 35-44, 45-54, 55-64 or 65-74). This gave a target of 12,800 patients, though for some categories (e.g. young female chronic bronchitics) this would be unattainable. Patients were selected from medical (including chest medicine), thoracic surgery, and radiotherapy wards. Controls were patients without one of the four index diagnoses, individually matched to cases on sex, age, hospital region and,

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when possible, hospital ward and time of interview. Subsequently, when final discharge diagnoses became available, they were used to reallocate cases and controls as necessary. Patients without a final diagnosis kept their provisional diagnosis. Where changes in case-control status occurred, patients were regrouped into new case-control pairs as appropriate. With the assistance of Sir Richard Doll and Mr Richard Peto, non-index diagnoses were classified as follows:

- class 1A 'definitely not smoking associated'
- class 1B 'probably not smoking associated'
- class 2A 'probably smoking associated'
- class 2B 'definitely smoking associated'

Controls with no final diagnosis were considered class 1B. Overall, there were 12,693 interviews carried out which resulted in 4,950 pairs with class 1 controls and 730 pairs with class 2 controls.

There were 3,832 interviews of married cases and controls where the passive smoking questionnaire was completed. In order to avoid substantial loss of data, due to one member of a pair not being married or not completing the passive smoking questionnaire, it was decided to ignore matching when analysing the passive smoking data and to compare each index group with the combined controls. Numbers by sex and case-control status are given in Table 1.

Table 1 Numbers of married hospital in-patients completing passive smoking questionnaires

	Male	Female	Total
Lung cancer	547	245	792
Chronic bronchitis	182	84	266
Ischaemic heart disease	286	221	507
Stroke	161	137	298
Controls:			
Class 1A and 1B*	839	713	1,552
Class 2A and 2B*	268	149	417
Total	2,283	1,549	3,832

*Other diseases were classified by degree of smoking association - class 1A: definitely not, class 1B: probably not, class 2A: probably, class 2B: definitely.

In the passive smoking part of the questionnaire, patients were asked when the marriage started, if and when it had ended; the number of manufactured cigarettes per day smoked by the spouse both during the last 12 months of marriage and also at the period of maximum smoking during the marriage; and whether the spouse ever regularly smoked hand-rolled cigarettes, cigars or a pipe during the marriage. For second or subsequent marriages, questions related to the first marriage to

give the longest latent interval between exposure and disease onset. The patients were also asked to quantify, according to a four-point scale (a lot, average, a little, not at all), the extent to which they were regularly exposed to tobacco smoke from other people prior to coming into hospital in 4 situations: at home; at work; during daily travel; during leisure time. In the main questionnaire, detailed questions were asked on smoking habits and on a whole range of possible confounding variables.

Follow-up study of spouses of non-smoking hospital in-patients

From the hospital study, there were 56 lung cancer cases who reported being lifelong non-smokers, who were married at the time of interview and who were not known to have been married previously. In a follow-up to the main study, an attempt was made to interview the spouses of these 56 cases and also the spouses of two life-long non-smoking controls for each case, individually matched for sex, marital status and 10-year age group and, as far as possible, hospital. Where multiple potential controls in the same hospital were available, those interviewed nearest in time to the case were selected. Where suitable controls in the same hospital were not available, those in the nearest hospital were chosen.

Because names and addresses of the patients were not recorded in the hospital study, it was necessary to go back to the hospital both to obtain this information and also to get permission to interview their spouses. Following some refusals both by the hospital and by the spouses, successful interviews were obtained from spouses of 34 cases (10 wives and 24 husbands) and 80 controls (26 wives and 54 husbands) whose condition was definitely or probably not related to smoking.

Interviewing was carried out between July 1982 and August 1983. The spouses were asked about their consumption of manufactured cigarettes, cigars and pipes (a) nowadays, (b) during the year of admission of the patient or (c) maximum during the whole of the marriage. The spouses were not asked about the smoking habits of the index patient. The spouses were also asked questions on age, occupation, social class and a range of other potential confounding factors.

Statistical methods

The statistical methods are based on classical procedures for analysis of grouped data derived from case-control studies (Breslow & Day, 1980). In general, the material has been examined as a $2 \times K \times S$ table, with K representing the levels of the

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risk factor of interest and *S* the number of strata used to take account of potential confounders.

Results presented are for the combined strata and show the relative risk (Mantel-Haenszel estimate) together with the significance of its difference from a base level (risk 1.0), and/or the dose-related trend. In analyses of the data collected in hospital, comparisons are made between cases with a particular index disease and all the controls with diseases definitely or probably not related to smoking. Six simple indices of passive smoke exposure were considered in these latter analyses, (i)-(iv) exposure at home, at work, during travel, during leisure, (v) spouse smoking manufactured cigarettes in the last 12 months, and (vi) spouse smoking manufactured cigarettes in the whole of the marriage. Bases for (ii) are reduced as not all patients worked. In addition, a combined index of passive smoke exposure was calculated by the unweighted sum of the four individual exposure indices (i)-(iv), counting 'not at all' as 0, 'little' as 1, 'average' as 2 and 'a lot' as 3.

Results

Lung cancer

The follow-up study concerned 56 lung cancer cases and 112 matched controls who reported never

having smoked in their hospital interview. Of these, there were 47 cases (15 male and 32 female) and 96 controls (30 male and 66 female) for whom some information on smoking habits of their spouses was available. Of these 143 patients, information on spouse smoking was available both from the spouse and from the patient for 59 (41%), from the spouse only for 55 (38%) and from the patient only for 29 (20%). Table II shows the estimated age-adjusted relative risk of lung cancer in relation to spouse smoking during the whole of the marriage, by sex, source of data, and period of smoking. None of the 9 relative risks shown in the table are statistically significant. When data for both sexes and both sources are considered, the estimated relative risks in relation to spouse smoking are close to 1 (1.11). For individual sexes or sources, where numbers of cases and controls are smaller, relative risks vary more from unity, but no consistent pattern is evident. Similar conclusions were reached, when analyses were based on smoking during the year of hospital interview. Here, the overall relative risk was again close to 1 (0.93 with limits 0.41-2.09).

Table III summarises concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly for the 59 patients with data from both sources. Discrepancies were seen for 9 spouses (15%) in respect of smoking at some time during marriage and in the case of 2

Table II Relationship between spouse's manufactured cigarette smoking during the whole of the marriage and risk of lung cancer among lifelong non-smokers (standardised for age)

Sex of patient	Spouse did not smoke		Spouse smoked		Relative risk (95% limits)
	Cases	Controls*	Cases	Controls*	
Based on interviews of the spouse in follow-up study (116 patients)					
Male	5	13	5	13	1.01(0.23-4.41)
Female	5	16	19	38	1.60(0.44-5.78)
Combined	10	29	24	51	1.33(0.50-3.48)
Based on interviews of the index patient in hospital (88 patients)					
Male	7	15	5	7	1.53(0.37-6.34)
Female	9	17	8	20	0.75(0.24-2.40)
Combined	16	32	13	27	1.00(0.41-2.44)
Based on both sources of information (143 patients)*					
Male	7	16	8	14	1.30(0.38-4.39)
Female	10	21	22	45	1.00(0.37-2.71)
Combined	17	37	30	59	1.11(0.51-2.39)

*Only controls included in follow-up study considered. *In this analysis the spouse was counted as a smoker if reported to be so either directly, by the spouse during follow-up interview, or, indirectly, by the patient in hospital. Note that the 59 patients for whom information on spouse smoking was available from both sources are included in all 3 analyses.

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Table III Concordance between spouse's manufactured cigarette smoking habits as reported directly and indirectly

	Sex of patient/case control status				
	Male		Female		Total
	Cases	Controls	Cases	Controls	
Spouse a smoker sometime in marriage according to:					
Subject and spouse:	2	6	5	13	26
Only subject:	1	0	0	3	4
Only spouse:	1	1	3	0	5
Neither:	3	11	1	9	24
% subject/spouse agreement:	71%	94%	67%	88%	85%
Spouse a smoker during year of hospital interview according to:					
Subject and spouse:	1	6	2	4	13
Only subject:	0	0	0	1	1
Only spouse:	1	0	0	0	1
Neither:	5	12	7	20	44
% subject/spouse agreement:	86%	100%	100%	96%	97%

spouses (3%) in respect of smoking during the year of hospital interview. There was no consistent pattern in the direction of discrepancy.

Table IV summarises the results of analyses carried out relating 7 indices of passive smoke exposure recorded in the hospital interviews to risk of lung cancer among lifelong non-smokers. Here the controls used for comparison are all never smoking patients with diseases classified as definitely or probably not associated with smoking who completed the passive smoking questionnaire.

Overall the results showed no evidence of an effect of passive smoking on lung cancer incidence among lifelong non-smokers. In male patients, relative risks were increased for some of the indices but numbers of cases were small and none of the differences approached statistical significance. In females, where numbers of cases were larger, such trends as existed tended to be negative and indeed were marginally significantly negative ($P < 0.05$) for passive smoking during travel and during leisure. For the combined sexes no differences or trends were statistically significant at the 95% confidence level; such trends as existed tending to be slightly negative. The relative risk in relation to the spouse smoking during the whole of the marriage was estimated to be 0.80 for the sexes combined, with 95% confidence limits of 0.43 to 1.50. Standardisation for working in a dusty job, the variable apart from smoking found to have the strongest association with lung cancer risk in the analyses described in Alderson *et al.* (1985), did not

affect the conclusion that passive smoking was not associated with risk of lung cancer among never smokers in our study.

Chronic bronchitis, ischaemic heart disease and stroke

Analyses similar to that shown in Table IV for lung cancer were also carried out for chronic bronchitis, ischaemic heart disease and stroke. Illustrative results for two of the indices are presented in Table V.

No significant relationship of any index of passive smoking to risk of the 3 diseases was seen. For the sexes combined, the relative risk in relation to the spouse smoking during the whole of the marriage was 0.83 for chronic bronchitis (95% confidence limits 0.31-2.20), 1.03 for ischaemic heart disease (limits 0.65-1.62) and 0.90 for stroke (limits 0.53-1.52). For stroke there was, in both sexes, an approximate 2-fold increase in risk for patients with a combined passive smoke index that was high (score of 5 to 12) compared with those where it was low (score of 0 or 1). However, numbers of cases with a high score were low (14 males and 7 females) and even for the sexes combined, the relative risk estimate of 2.18 was not statistically significant (limits 0.86-5.48). In interpreting this finding, it should be noted that active smoking was not found to be clearly related to stroke in the main study (Alderson *et al.*, 1985), rendering a two-fold increase in relation to passive smoking *a priori* unlikely.

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Table IV Relationship between various indices of passive smoke exposure and risk of lung cancer among lifelong non-smokers (standardized for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	Male patients			Female patients			Sexes combined		
	Cases	Controls	R	Cases	Controls	R	Cases	Controls	R
At home									
Not at all	9	101	1	21	192	1	30	293	1
Little	2	21	1.22	6	65	0.92	8	86	0.98
Average/a lot	1	11	1.11	5	61	0.81	6	72	0.86
At work									
Not at all	3	40	1	12	113	1	15	153	1
Little	6	29	3.24	3	26	1.18	9	55	1.82
Average/a lot	1	29	0.46	0	19	0.0	1	48	0.19
During travel									
Not at all	8	101	1	28	238	1	36	339	1
Little	3	16	2.06	2	51	0.33	5	67	0.64
Average/a lot	0	13	0.00	0	13	0.00	0	26	0.00
						Trend (negative) P<0.05			
During leisure									
Not at all	3	45	1	15	116	1	18	161	1
Little	4	48	1.12	14	107	1.05	18	155	1.06
Average/a lot	5	39	3.18	2	95	0.18	7	134	0.59
						Trend (negative) P<0.05			
Combined index*									
Score 0-1	1	27	1	10	75	1	11	102	1
Score 2-4	7	55	4.34	5	61	0.63	12	116	1.08
Score 5-12	2	15	3.20	0	21	0.00	2	36	0.50
Spouse smoked man, cigs in last 12 months									
No	10	105	1	20	193	1	30	298	1
Yes	2	29	0.96	11	122	0.76	13	151	0.79
Spouse smoked man, cigs in whole of marriage									
No	7	93	1	13	89	1	20	182	1
Yes	5	40	2.47	19	229	0.55	24	269	0.80

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

Discussion

Over the past 4 years there has been considerable research interest in the relationship between passive smoking and risk of lung cancer in nonsmokers. While some studies have claimed a positive effect (Hirayama, 1981; Trichopoulos *et al.*, 1981; Correa *et al.*, 1983; Garfinkel *et al.*, 1985; Gillis *et al.*, 1984; Knott *et al.*, 1983), others (Brunner *et al.*, 1984; Chan, 1982; Garfinkel, 1981; Kabat and Wynder, 1984; Koo *et al.*, 1984) have found no significant relationship. Relative risks of lung cancer for non-smoking women married to smokers compared to non-smoking women married to non-smokers range from somewhat over 2 in the Trichopoulos and Correa studies to around 0.75 in

the Brunner and Chan studies. The weighted relative risk from these studies has been estimated by us as approximately 1.3. While there is, therefore, a tendency for a small positive association between passive smoking and lung cancer, recent reviews of these data (Lee, 1984; Lehnert *et al.*, 1984) have concluded that overall there is no reliable scientific evidence of a causal relationship between passive smoking and lung cancer. In these reviews a number of general points have been made.

First, dosimetric studies have shown that, in cigarette-equivalent terms, passive smoking only results in a relatively small exposure to the non-smoker. Hugod *et al.* (1978), for example, showed that even under quite extreme conditions the time taken for a non-smoker to inhale the equivalent of

Table V Relationship between two indices of passive smoke exposure and risk of chronic bronchitis, ischaemic heart disease and stroke among lifelong non-smokers (standardised for age and, for spouse smoking, whether the marriage was ongoing or ended)

Passive smoke exposure index/level	Male patients			Female patients			Sexes combined		
	Cases	Controls	R	Cases	Controls	R	Cases	Controls	R
Chronic bronchitis									
Combined index*									
Score 0-1	1	27	1	7	75	1	8	102	1
Score 2-4	2	55	0.83	4	61	1.05	6	116	1.00
Score 5-12	1	15	1.90	1	21	1.03	2	36	1.30
Spouse smoked man cigs. in whole of marriage									
No	8	93	1	4	89	1	12	182	1
Yes	1	40	0.34	13	229	1.22	14	269	0.83
Ischaemic heart disease									
Combined index*									
Score 0-1	15	27	1	23	75	1	38	102	1
Score 2-4	12	55	0.43	9	61	0.59	21	116	0.52
Score 5-12	3	15	0.43	4	21	0.81	7	36	0.61
Spouse smoked man cigs. in whole of marriage									
No	26	93	1	22	89	1	48	182	1
Yes	15	40	1.24	55	229	0.93	70	269	1.03
Stroke									
Combined index*									
Score 0-1	5	27	1	19	75	1	24	102	1
Score 2-4	10	55	1.24	10	61	0.86	20	116	0.97
Score 5-12	4	15	1.77	7	21	2.44	11	36	2.18
Spouse smoked man cigs. in whole of marriage									
No	18	93	1	19	89	1	37	182	1
Yes	6	40	0.84	49	229	0.92	55	269	0.90

*Based on sum of 0 = not at all, 1 = little, 2 = average, 3 = a lot for at home, at work, during travel, during leisure.

one cigarette would be 11 hours as regards particulate matter and 50 hours as regards nicotine. Similarly, Jarvis *et al.* (1985) have shown that the increase in salivary cotinine in relation to passive smoke exposure is less than 1% of that in relation to active smoke exposure. Extrapolating linearly from the 10-fold relative risk of lung cancer in relation to active smoking would therefore predict a relative risk in relation to passive smoking less than 1.1, while a quadratic extrapolation, as suggested by Doll and Peto (1978) would predict a lower risk still. The conflict between the dose and the claimed response is particularly clear for the results of Hirayama (1981) who found a similar effect on lung cancer for passive smoking as for active smoking of 5 cigarettes a day.

Second, all the studies suffer from weak exposure data, most studies only obtaining information on the spouse's smoking habits and none obtaining objective data by measurement of ambient levels of smoke constituents in the air of the home or

workplace and/or of concentrations of constituents in body fluids.

Third, no studies adequately take into account the possibility that misclassification of active smokers as non-smokers may have consistently biased relative risk estimates upward. Active smokers have a high relative risk of lung cancer and spouses' smoking habits are positively correlated. Because of this, it can be shown that if a relatively small proportion of smokers deny smoking, this results in an apparent elevation in risk of lung cancer in 'non-smokers' married to smokers compared to 'non-smokers' married to non-smokers, even when no true effect of passive smoking exists. A demonstration that this source of bias is of real importance can be found in the study of Garfinkel *et al.* (1985). Based on unvalidated smoking data taken from hospital notes, a relative risk of lung cancer in relation to husband's smoking at home of 1.66 was calculated, with relative risks of at least 1.3 seen in relation to each

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level of husband's cigarette smoking and in relation to husband's cigar and pipe smoking. When additional sources of information on smoking habits were used, the overall relative risk was reduced to a marginally significant 1.31 with an elevated risk only really discernible in relation to heavy cigarette smoking by the husband. Even here, it is notable that the elevation in risk was not evident when smoking data were obtained from the subject or her spouse directly, but was only evident when the data were obtained from the daughter or son or another informant, i.e. from those people who were less likely to have known the full smoking history. The lower relative risk may still have arisen wholly or partly as a bias resulting from misclassification of smoking habits.

Fourth, many of the studies are open to specific criticisms. For example, the conclusion of Gillis *et al.* (1984) that male lung cancer deaths in non-smokers rose from 4 per 10,000 in those not exposed to passive smoke to 13 per 10,000 in those who were exposed was based on a total of only 6(!) deaths and was not statistically significant. Also the claim by Knott *et al.* (1983) of a relationship between passive smoking and lung cancer in non-smoking women was based simply on the observation that the proportion of female non-smoking lung cancer patients living together with a smoker exceeded the proportion of male smokers as reported in the previous microcensus, ignoring *inter alia* the fact that in many families women live with more than just their husbands.

In the present study no significant relationship of passive smoking to lung cancer incidence in lifelong non-smokers was seen, either in the analyses based on the information collected in hospital or in subsequent inquiry of the spouses or both. It must be pointed out, however, that the number of lung cancer patients who had never smoked was rather small so that, though our findings are consistent with passive smoking having no effect on lung cancer risk at all, they do not exclude the possibility of a small increase in risk, though the upper 95% confidence limit of 1.50 for the estimate of 0.80 (Table IV) in relation to the spouse smoking during the whole of the marriage is not consistent with some of the larger increases claimed by Hirayama (1981, 1984) Trichopoulos *et al.* (1981, 1983) and Correa *et al.* (1983).

Though the number of lung cancer patients who had never smoked is small, varying around 30-50 depending on the analysis, this number is not very different from that reported in a number of other studies, e.g. the findings of Correa *et al.* (1983) were based on only 30, while those of Trichopoulos *et al.* (1981), even when updated (Trichopoulos *et al.*, 1983) were based on only 77. The difficulty of obtaining an adequate sample size is underlined

when one considers that in our study the 44 never smoking lung cancer patients who completed passive smoking questionnaires in hospital were extracted from a total of 792 lung cancer patients. It would need a very large research effort to increase precision substantially, and even then one would have to take care that the magnitude of any biases did not exceed the magnitude of the effect one was looking for.

The two major prospective studies which have so far reported findings on passive smoking (Hirayama, 1981; Garfinkel, 1981) were not actually designed to investigate this issue and, as a result, could only use spouse's smoking as an index of exposure. Our study, on the other hand, though not able to monitor exposure objectively, as would have been preferable, was able to look at passive smoking in a wider context, by asking about the extent of exposure at home, at work, during travel and at leisure. Although the answers to these questions were subjective, and could have exhibited some bias, their inclusion perhaps allows greater confidence in the conclusions.

It was interesting that, of the 59 patients for whom spouse's cigarette smoking habits were obtained from both the spouse and the patients, there were 9 (15%) patients for whom there was disagreement as to whether the spouse had been a smoker at some time during the marriage. It seems reasonable to suppose that some of these were in fact smokers and may have been erroneously classified as non-smokers had only one source of information been used. It was also noteworthy that there was quite a strong correlation in our study between active and passive smoking. As illustrated in Table VI, current smokers were considerably more likely to be exposed to passive smoke exposure at home (from sources other than their own cigarettes) than were never or ex-smokers. As noted above, this correlation, coupled with some misclassification of smokers as non-smokers, may spuriously inflate the estimate of risk related to passive smoking. It is important to carry out further studies to obtain more accurate information on reliability of statements about smoking habits because of this possibility of bias.

Little other evidence is available concerning the relationship between passive smoking and risk of the other smoking-associated diseases in (adult) non-smokers and much of this is open to criticism. In his original paper, Hirayama (1981) presented relative risks of death for various diseases for non-smoking women according to the husband's smoking habits. Based on a total of 66 deaths, a slight positive trend for emphysema and asthma was not significant, while, based on a total of 406 deaths, no indication of a trend at all was seen for ischaemic heart disease. In a later paper, based on

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Table VI Relative odds of having passive smoke exposure at home according to patient's own manufactured cigarette smoking habits (standardised for age base - combined class 1 and 2 controls)

Own smoking habits	Relative odds (95% confidence limits)	
	Male	Female
Never	1	1
Ex	1.25(0.86-1.81)	1.26(0.86-1.85)
Current	4.00(2.67-5.94)	2.51(1.74-3.62)
Chi-squared for trend (2df)	57.81	25.34
P	<0.001	<0.001

only a further 88 ischaemic heart disease deaths. Hirayama (1984) reported a slight positive trend in risk, but this was not statistically significant. Garland *et al.* (1985), in a small prospective study, reported a 15-fold higher risk of ischaemic heart disease in non-smoking Californian women whose husbands were current or former smokers compared with those whose husbands were never smokers, but this enormous and implausible relative risk was only significant at the 90% confidence level and had very wide confidence limits, being based on only 2 deaths in women whose husbands were current smokers. Sandler *et al.* (1985), in a case-control study carried out in North Carolina, reported a strong relationship between risk of cancer of all sites and passive smoking. This study has been criticised by Lee (1985) who notes that it is basically implausible that passive smoking should increase risk of cancers not associated with active smoking. Lee also criticised the method of analysis, showing that no association with cancer risk would be found if a more standard method of analysis was used. Vanderbroucke *et al.* (1984), based on a 25 year follow-up of 1,070 Amsterdam married couples, recently reported that passive smoking was associated with some decrease in total mortality.

There is evidence indicating that young children whose parents smoke have an excess incidence of respiratory symptoms and some reduction in pulmonary function. Reviewing this evidence, Lee (1984) noted that the interpretation of the association is fraught with difficulties and that other possible explanations, including social class related factors, parental neglect, nutrition, cross-infection and smoking during pregnancy, had not been taken into account adequately, so that a causal effect of passive smoking could not be inferred. The relevance of these findings to chronic bronchitis or other diseases in adults is in any case not clear.

Our analyses showed no significant effect of

passive smoking on lifelong non-smokers as regards risk of chronic bronchitis, ischaemic heart disease or stroke. In all the analyses relating the various indices of passive smoke exposure to these diseases, no significant differences were seen and slight decreases in risk were as common as slight increases.

While more data would be desirable for these diseases, lung cancer continues to be the major smoking associated disease for which passive smoking comes under suspicion. Since all the difficulties of carrying out good research have clearly still not yet been overcome, further research is certainly needed. Our findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

Any views expressed in this paper are those of the authors and not of any other person or company.

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Koo, L.C., Ho, J.H.C., Matsuki, H., Shimizu, H., Mori, T., Tominaga, S. "A comparison of the prevalence of respiratory illnesses among nonsmoking mothers and their children in Japan and Hong Kong" Am Rev Respir Dis 138(2): 290-295, 1988.

SUMMARY: Previous epidemiologic studies have associated symptoms of chronic bronchitis and other respiratory diseases with the risk for lung cancer. To assess the possible precursor or premonitory role of these conditions for lung cancer among nonsmokers, a comparison of the prevalence rates of these conditions in 2 urban industrialized communities (Hong Kong and a Tokyo suburb) with a 300% difference in female lung cancer incidence rates was conducted. A community survey of 314 nonsmoking mothers and their children in Hong Kong, and 243 mothers and children in Japan showed that the prevalence of reported chronic cough and sputum symptoms was 10 or more times higher in Hong Kong than in Japan. The disparity in the rates of respiratory diseases/symptoms was most apparent in the comparison of children. Occupational exposure to dust or fumes and larger household sizes were found to be associated with higher levels of respiratory illnesses among the Hong Kong mothers. The much higher prevalence rates of respiratory symptoms among Hong Kong than among Japanese subjects correlated with each community's female lung cancer incidence rates of 27.1 versus 8.1/100,000, respectively.

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A Comparison of the Prevalence of Respiratory Illnesses among Nonsmoking Mothers and Their Children in Japan and Hong Kong^{1,2}

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and SUKETAMI TOMINAGA

Introduction

A previous study on lung cancer among Hong Kong Chinese females found that patients with lung cancer were more likely to report a previous history of chronic cough or phlegm expectoration than were age-matched control subjects (1). These results were applied to those who had ever or never smoked, and a dose-response relationship was found between increasing years of experiencing these symptoms and risk for lung cancer.

The association of a previous history of respiratory diseases such as chronic bronchitis and pneumonia with lung cancer was first reported by Doll and Hill in their 1952 study on the etiology of lung cancer (2). Subsequently, other studies (3-5) also reported this association, although most did not segregate the effects of a past history of active smoking and the occurrence of these diseases.

Because Hong Kong Chinese females tend to have notably high lung cancer incidence rates, with a 1982 world age-adjusted incidence rate of 27.1 per 100,000 (6), a comparative study of females from a low incidence area such as Japan, with a world age-adjusted incidence rate of only 8.1 per 100,000 (7) for 1975-1979 in the Kanagawa Prefecture, might shed some light on this possible etiologic association. Both societies are racially similar and share a predominantly urban, industrialized environment. Yet their cultural habits and diets are sufficiently different to raise the possibility that their respective exposures to a variety of pollutants or protectors account at least in part for the 300% difference in their lung cancer rates.

The purpose of this cross-sectional study was to compare the prevalence rates of respiratory illnesses among children and mothers residing in 2 communities, one in Japan and the other in Hong Kong. Only subjects with no previous his-

SUMMARY Previous epidemiologic studies have associated symptoms of chronic bronchitis and other respiratory diseases with the risk for lung cancer. To assess the possible precursor or premonitory role of these conditions for lung cancer among non smokers, a comparison of the prevalence rates of these conditions in 2 urban industrialized communities (Hong Kong and a Tokyo suburb) with a 300% difference in female lung cancer incidence rates was conducted. A community survey of 314 nonsmoking mothers and their children in Hong Kong, and 243 mothers and children in Japan showed that the prevalence of reported chronic cough and sputum symptoms was 10 or more times higher in Hong Kong than in Japan. The disparity in the rates of respiratory diseases/symptoms was most apparent in the comparison of children. Occupational exposure to dust or fumes and larger household sizes were found to be associated with higher levels of respiratory illnesses among the Hong Kong mothers. The much higher prevalence rates of respiratory symptoms among Hong Kong than among Japanese subjects correlated with each community's female lung cancer incidence rates of 27.1 versus 8.1/100,000, respectively. AM REV RESP DIS 1988; 138:290-295

tory of active smoking were included. We wanted to know if differences found in their respective prevalence rates of respiratory illnesses would help explain the differing lung cancer incidence rates in the 2 populations. In addition, we wanted to know if these data could point to possible precursor respiratory conditions that might increase the individual's susceptibility to environmental carcinogens or that might indicate early premonitory symptoms since lung cancer is usually detected decades later.

Methods

Japanese Subjects

In July 1982, students from Grades 2 through 6 attending 2 public primary schools around the Tokyo area were surveyed. One school was located at the Sugunami-ward in Tokyo and the other in Aikawa in the Kanagawa Prefecture, which is located about 50 kilometers west of Tokyo. The mothers of the surveyed children were also studied. These subjects were chosen from these districts because they would be representative of Japanese living in urban and rural environments in Japan. The Sugunami-ward is a typical urban residential area with several heavily traveled roads traversing the district. The Aikawa area is characteristically rural without major factories and heavily traveled roads.

The response rate was 99.6% for the 457

children and 88.2% for their 403 mothers/guardians. Out of this sample, the following data were not included in this analysis: incompletely answered questionnaires ($n = 38$), guardians who were not mothers of the children ($n = 11$), any who reported a previous history of active smoking ($n = 68$), and, in situations where 2 or more children from the same family were surveyed and attended the same school ($n = 95$), only 1 of the children was randomly selected. Thus, the results from 243 mother-child pairs were analyzed for this study.

Hong Kong Subjects

A government-subsidized primary school in the Ngau Tau Kok area of the Kwun Tong

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TABLE 1
AGE DISTRIBUTION AMONG MOTHERS

Age (yr)	Hong Kong		Japan	
	(n)	(%)	(n)	(%)
< 30	18	5.7	13	5.4
31-35	99	31.5	79	33.1
36-40	123	39.2	87	36.4
41-45	39	12.4	49	20.5
46-50	27	8.6	10	4.2
≥ 51	8	2.5	1	0.4
Unknown			4	
Total	314		243	
Mean age*	37.8		39.3	

* *t* test, *p* value = 0.412

district of Hong Kong was selected in cooperation with the local government's Department of Education to represent subjects from a working class neighborhood. The site is surrounded by public housing in high-rise buildings and by small stores, and is within a few blocks of the small- and medium-sized factories that are common in this district.

Initially, 2 classes from each grade of 2 to 6 were planned for the study since each class averaged 36 students, and these numbers would approximate the age and sex distribution of the Japanese subjects. However, after data collection began, it was realized that some students in different classes were siblings, so an additional class in Grade 4 was included in the study. Thus, a total of 11 classes, i.e., 390 children and mothers were contacted for the study. The response rate for the return of the questionnaire was 100% for the children and 97% for their mothers/guardian (11 did not return the questionnaire). Using the same inclusion criteria as those for the Japanese subjects, 314 mother-child pairs were included in this analysis. To simulate the summer weather conditions of the Japanese collection time, the survey was conducted from May 20 to 30, 1985. The mean temperature and humidity in Hong Kong during the data collection period was 27°C and 81% humidity. The same data for Tokyo during July 1982 was 22°C and 77%, respectively. The Hong Kong data were collected in late May instead of July because the students would be off for summer vacations and thus not accessible.

Data Collection Forms

A modified version of the questionnaires originally developed by the American Thoracic Society Division of Lung Disease (ATS-DLD) (8) and the British Medical Research Council (BMRC) (9) to survey the prevalence of respiratory diseases was used. Questions were asked on the occurrence of the following: chronic cough or phlegm of ≥ 3 months duration (to eliminate those associated with acute upper respiratory tract infections), bronchitis, pneumonia, asthma, tuberculosis, allergic rhinitis, and other chest diseases.

The version for the children also included

TABLE 2
AGE DISTRIBUTION AMONG CHILDREN

Age (yr)	Hong Kong		Japan	
	(n)	(%)	(n)	(%)
6	0		11	4.5
7	10	3.2	44	18.1
8	46	14.6	20	8.2
9	54	17.2	45	18.5
10	80	25.5	29	11.9
11	48	15.3	82	33.7
12	67	21.3	12	4.9
13	9	2.9	—	
Total	314		243	
Mean age*	10.1		9.4	
Girls, %†		48		46

* *t* test, *p* value = 0.0001† *t* test, *p* value = 0.588

questions on sources and amounts of passive smoking exposure, and whether the child participated in home cooking activities. These questionnaires were distributed to the children at school and taken home with instructions that it be answered for the child by the mother or female guardian.

The version for the mothers included more detailed questions on cooking activities, active smoking history, and exposure to dust or fumes in the workplace. These questionnaires were distributed to the children at school with instructions that they should take them home for their mothers to fill out.

Data Analysis

The data collected in the questionnaires were coded and then processed by computer using the SPSS-X statistical package. Because the questionnaire asked about respiratory symptoms (i.e., cough, sputum, wheezing) and respiratory diseases (i.e., pneumonia, allergic rhinitis, bronchitis, asthma, tuberculosis), both were covered under the term "respiratory illnesses." These terms are distinguished

in this study because "respiratory symptoms" is a lay term that is easier for the subjects to identify with, whereas "respiratory diseases" would mean that a physician had diagnosed such a condition.

Analysis of the data included descriptive, comparative, and analytical work. In comparing the results between subjects from Hong Kong versus those from Japan, *t* tests or chi-square tests were usually done to estimate the statistical significance of the findings. Analysis on the relationship of multiple illnesses per person and various exposure categories utilized Pearson's goodness of fit test. A test for linear trend in the proportions was done when dose-response relationships were suggested (10). To statistically assess the risk among the exposed group versus the unexposed group, the following were calculated: relative risks as the ratio of these 2 proportions; attributable risk as the percentage of the overall risk in the exposed group, and the population-attributable risk as the difference in risk among the whole population (which we assume the entire sample represented) and the risk in the unexposed group (10).

Results

The age distribution of the 314 Hong Kong Chinese mothers and 243 Japanese mothers is shown in table 1. The Hong Kong Chinese mothers tended to be slightly younger, with a mean age of 37.8 versus 39.3 yr among the Japanese mothers, but these differences were not statistically different (*t* test, *p* value = 0.41). On the other hand, the 314 Hong Kong school children were slightly older than their Japanese counterparts (table 2), with the mean age of the former being 10.1 yr and that for the latter being 9.4 yr, which was statistically significant (*t* test, *p* value = 0.0001). The sex ratio for the children was not significantly

TABLE 3
PREVALENCE OF SELF-REPORTED RESPIRATORY ILLNESSES AMONG NON-SMOKING MOTHERS

Respiratory Symptom/Disease	Prevalence (%)		Chi-Square p value
	Hong Kong (n = 314)	Japan (n = 243)	
Chronic cough ≥ 3 months, %	5.7	0.4	0.006
Chronic phlegm ≥ 3 months, %	8.0	0.4	0.000
Cough and phlegm ≥ 3 months, %	3.2	0.4	0.0197
Cough or phlegm ≥ 3 months, %	10.5	0.4	0.0025
Bronchitis, %	7.6	5.8	0.3823
Ever had pneumonia, %	1.0	2.9	0.0897
Ever had asthma, %	1.3	2.9	0.1765
Ever had tuberculosis, %	1.6	2.1	0.5817
Ever had allergic rhinitis, %	11.5	12.4	0.7498
Ever had other chest diseases, %	0.3	1.2	0.2041
≥ 1 of the above chest illnesses, %	24.8	20.9	0.0254
Chest illnesses per sick mother, mean n	1.49	1.29	0.0371

* *p* value by *t* test

TABLE 4
PREVALENCE OF RESPIRATORY ILLNESSES AMONG CHILDREN
AS REPORTED BY THEIR MOTHERS

Respiratory Symptom/Disease	Prevalence (%)		
	Hong Kong (n = 314)	Japan (n = 243)	Chi-Square p Value
Cough \geq 3 months, %	7.0	0.4	0.0001
Phlegm \geq 3 months, %	9.2	0.4	0.0000
Cough and phlegm, %	3.5	0	—
Cough or phlegm, %	12.8	0.8	0.0000
Cough or phlegm, yr/person	4.7	3.5	0.742*
Wheezing \geq 3 months, %	7.6	1.7	0.0013
Wheezing, yr/person	4.8	6.8	0.180*
Ever had allergic rhinitis, %	9.2	11.1	0.4554
Ever had pneumonia, %	8.0	0	—
Ever had asthma, %	8.3	10.7	0.3304
\geq 1 of the above chest illnesses, %	25.2	18.7	0.066
Chest illnesses per sick child, mean \pm n	1.96	1.31	0.0001*

* p value by χ^2 test

different for the 2 groups, with 48% of the Hong Kong children and 46% of the Japanese children being girls (t test, p value = 0.59).

The prevalence rates among mothers reporting a previous history of respiratory illnesses is shown in table 3. Among Chinese mothers, 5.7% ($n = 18$) reported a previous history of chronic cough, and 8.0% ($n = 25$), a history of chronic phlegm expectoration lasting 3 or more months. This contrasted with only 1 Japanese mother (0.4%) who reported having both such symptoms. For the other respiratory diseases, the prevalence rates between the 2 groups did not reach statistical significance ($p \leq 0.05$). In general, there was a tendency for more Hong Kong mothers to report a previous history of chest problems (24.8 versus 20.9%); among those who had such diseases, Hong Kong mothers had more illnesses per person (1.49 versus 1.29) than did Japanese mothers. There was no relationship between the prevalence rates of respiratory illnesses and age of the mother in either population (chi-square, p value = 0.236 for Hong Kong mothers and 0.274 for Japanese mothers).

The prevalence of respiratory illnesses among children was similar to that of their mothers (table 4). One (0.4%) Japanese child was reported by the mother to be suffering from chronic cough, and another (0.4%) was reported to have chronic phlegm, whereas among the Hong Kong children these percentages were 7.0% ($n = 22$) and 9.2% ($n = 29$), respectively. When the 2 symptoms were combined, 12.8% ($n = 40$) of the Hong Kong children had one or both symptoms, whereas this was true for only 0.8% ($n = 2$) of

the Japanese children. All of these differences were statistically significant.

Among the other respiratory illnesses for the children, those in Hong Kong had statistically higher frequencies of wheezing (7.6 versus 1.7%) and pneumonia (8.0 versus 0%) than did their Japanese counterparts. The reported rates for allergic rhinitis and asthma were not statistically different for the 2 groups.

In the summary measurements, 25.2% of the Hong Kong children had one or more of the surveyed respiratory illnesses versus 18.7% among the Japanese children ($p = 0.066$). Moreover, among those with such illnesses, the former group had a significantly larger mean number of problems per child (1.96) than did the latter (1.31).

The distribution of multiple illnesses within a single individual in the 2 areas is shown in table 5. Hong Kong mothers

TABLE 5
RELATIONSHIP BETWEEN THE FREQUENCY
OF RESPIRATORY ILLNESSES BETWEEN
MOTHER CHILD IN HONG KONG
AND IN JAPAN*

Illnesses per Child (n)	Illnesses per Mother (n)		
	0	1+	Total
Hong Kong			
0	186	48	234
1+	49	30	79
Total	235	78	313
Relative risk = 1.85†			
Japan			
0	157	33	190
1+	28	15	43
Total	185	48	233
Relative risk = 2.00‡			

* The presence of the following respiratory illnesses unrelated to cold/flu: cough \geq 3 months, phlegm \geq 3 months, wheezing, pneumonia, asthma, allergic rhinitis, bronchitis, TB, and other chest diseases.

† Pearson's correlation coefficient 0.18; p value = 0.209.

‡ Pearson's correlation coefficient 0.17; p value = 0.205.

and children consistently had higher percentages of such individuals than did the Japanese. This discrepancy was most apparent among the children, with 24 Hong Kong children (7.7%) having 3 or more respiratory illnesses versus only 1 Japanese child (0.4%) with such a history, and a comparison of their mean number of illnesses per child was highly significant ($p = 0.0001$).

The frequency of illnesses in the mothers was related to that reported for their children as shown in table 6. In both populations, mothers who reported one or more respiratory illnesses for themselves were about twice as likely to report such illnesses in their children. Pearson's goodness of fit test showed this relationship to be highly significant.

TABLE 5
FREQUENCY OF MULTIPLE RESPIRATORY ILLNESSES AMONG MOTHERS AND
CHILDREN IN HONG KONG AND JAPAN

Illnesses per Mother† (n)	Hong Kong Mothers		Japanese Mothers		Illnesses per Child† (n)	Hong Kong Children		Japanese Children	
	(n)	(%)	(n)	(%)		(n)	(%)	(n)	(%)
0	235	75.1	185	79.4	0	234	74.8	190	81.5
1	54	17.3	39	16.7	1	45	14.4	30	12.9
2	14	4.5	4	1.7	2	10	3.2	12	5.2
3	7	2.2	5	2.1	3	11	3.5	1	0.4
4+	3	0.9	—	—	4+	13	4.2	—	—
Total	313	100	233	99.9‡		313	100.1‡	233	100
Mean	0.37		0.27			0.69		0.24	

* The presence of the following respiratory illnesses unrelated to cold/flu: cough \geq 3 months, phlegm \geq 3 months, pneumonia, allergic rhinitis, bronchitis, asthma, TB, and other chest diseases.

† The presence of the following respiratory illnesses unrelated to cold/flu: cough \geq 3 months, phlegm \geq 3 months, wheezing, pneumonia, asthma, allergic rhinitis.

‡ Due to rounding off, the total sum was not 100%.

TABLE 7
RELATIONSHIP OF OCCUPATIONAL DUST OR GAS/FUME EXPOSURE WITH
RESPIRATORY ILLNESSES AMONG HONG KONG MOTHERS*

Exposure at Work	Total Number of Mothers	Mothers with ≥ 1 Respiratory Illnesses†		
		(n)	(%)	Relative Risk
Dust				
No exposure	246	55	22.4	1.00
Mild	39	12	30.8	1.38
Moderate	25	9	36.0	1.61
Severe	4	2	50.0	2.23
Total exposed	68	23	33.8	1.51
Gas				
No exposure	278	63	22.7	1.00
Mild	23	9	39.1	1.72
Moderate	11	5	45.5	2.00
Severe	2	1	50.0	2.20
Total exposed	36	15	41.7	1.84

* Linear trend p value < 0.05 . Pearson's correlation coefficient significance: p value presence and absence of illnesses: dust = 0.017; gas = 0.007. Exact number of illnesses: dust = 0.007; gas = 0.0008.

† The presence of the following respiratory illnesses unrelated to cold/flu: cough ≥ 3 months; pneumonia; allergic rhinitis; bronchitis; asthma; TB; and other chest diseases.

TABLE 8
COMPARATIVE PROFILES OF HONG KONG AND JAPANESE
MOTHERS AND CHILDREN†

Lifestyle Variable	Hong Kong		Japan		Chi-Square p Value
	(n)	(mean)	(n)	(mean)	
Mother currently works outside the home	106	33.9%	68	28.0%	0.138
Father currently smokes	110	35.6%	146	60.1%	0.0000
Home has ventilated cooking*	251	79.9%	192	79.2%	0.789
Mean household size	314	5.31	243	4.54	0.000†

* Cooking area has electric ventilating fan or cooking hood.

† p value by t test.

To understand the role of occupational exposures, the Hong Kong mothers were asked in the questionnaire whether they had ever worked for a year or more in places where they were exposed to noticeable levels of dust/smoke or gases/fumes, the degree of such exposure, where such exposure occurred, and what they did. Analyses of all the variables showed that the frequency of respiratory illnesses among Hong Kong mothers was highly related to their reports of previous exposure to dust or gas fumes (table 7) in the workplace.

Overall, some 21.7% ($n = 68$) of the total sample of Hong Kong mothers reported a previous history of occupational exposure to dust, and 11.5% ($n = 36$) to gas/fumes. The percentages of exposed mothers with one or more respiratory illnesses increased proportionately with the degree of reported severity of exposure to such air pollutants in a dose-response manner. Among those exposed to severe levels of either pollutant, the attributable risk was calculated to be

55%. Gas fumes seemed to exert a larger effect than did dust, as the attributable risk was 45.6% for the former versus 33.8% for the latter.

Although the same questions were not asked in the Japanese survey, data on Japanese mothers currently employed in dusty industries such as mining showed no relationship with their prevalence of respiratory illnesses. In addition, when comparing the lifestyle profiles of the 2 populations (table 8), it can be seen that mothers in Japan were less likely to work outside the home, so that their likelihood of being exposed to such occupational exposures would be less than that of the Hong Kong mothers.

In terms of possible sources of indoor air pollutants in the home, the data did not help explain the discrepancy in prevalence rates in the 2 populations. Some 60% of the Japanese fathers were current smokers versus only 36% of the Hong Kong fathers. Although cooking styles are greatly different between the 2 populations, with Chinese cooking methods more likely to produce cooking fumes because of the stir-fry method, the percentages of kitchens with mechanical ventilation fans/hoods was the same in both populations, i.e., 79 to 80%.

It was interesting to note that the mean household size was statistically different ($p = 0.000$), with Hong Kong families averaging 5.31 persons versus 4.54 persons in Japan. The effects of family size on the frequency of respiratory illnesses are shown in table 9. There was a tendency for Hong Kong mothers living in larger households to report more respiratory illness than those living in smaller ones. However, such was not the case for the Japanese mothers. Moreover, among the Hong Kong mothers, no relationship was found between household density, i.e., the total number of people in the family

TABLE 9
RELATIONSHIP OF FAMILY SIZE TO RESPIRATORY ILLNESSES
AMONG HONG KONG AND JAPANESE MOTHERS*

Household Size	Total Number of Mothers	Mothers with ≥ 1 Respiratory Illnesses†		
		(n)	(%)	Relative Risk
Hong Kong				
Small, < 4	100	22	22.0	1.00
Medium, 5 to 6	155	37	23.9	1.09
Large, 7+	59	19	32.2	1.46
Total	314	78	24.8	
Japan				
Small, < 3	28	5	17.9	1.00
Medium, 4 to 5	175	40	22.9	1.28
Large, 6+	40	9	22.5	1.26
Total	243	54	22.2	

* Pearson's correlation coefficient significance and p values. Presence and absence of illnesses: Hong Kong $r = 0.024$, $p = 0.33$; in Japan $r = 0.025$, $p = 0.35$. Exact number of illnesses: Hong Kong $r = 0.076$, $p = 0.09$; in Japan $r = 0.034$, $p = 0.30$.

† The presence of the following respiratory illnesses unrelated to cold/flu: cough ≥ 3 months; pneumonia; allergic rhinitis; bronchitis; asthma; TB; and other chest diseases.

TABLE 10
RELATIONSHIP OF HOUSEHOLD DENSITY WITH RESPIRATORY
ILLNESSES AMONG HONG KONG MOTHERS*

People per Room (n)	Total Number of Mothers	Mothers with ≥ 1 Respiratory Illnesses†		
		(n)	(%)	Relative Risk
Low: ≤ 2.49	81	20	24.7	1.00
Medium: 2.5 to 3.5	105	23	21.9	0.89
High: > 3.5	128	35	27.4	1.11
Total	314	78	24.8	

* Pearson's correlation coefficient and *p* values: presence and absence of illnesses $r = 0.031$, $p = 0.29$; exact number of illnesses $r = 0.008$, $p = 0.44$.

† The presence of the following respiratory illnesses unrelated to cold/flu: cough ≥ 3 months; phlegm ≥ 3 months; pneumonia; allergic rhinitis; bronchitis; asthma; TB; and other chest diseases.

divided by the number of rooms they occupied, and the frequency of respiratory illnesses (table 10). The Japanese data did not contain information on household density for comparative analysis.

Discussion

The findings of this preliminary epidemiologic study on the prevalence of respiratory illnesses among never-smoked mothers and children in Hong Kong and Tokyo suggest that such illnesses are much more common in Hong Kong. Hong Kong subjects were 10 or more times more likely than their Japanese counterparts to report symptoms of chronic cough and phlegm expectoration exceeding 3 months duration.

The differences in reported frequencies of respiratory illnesses were greatest in the comparison of school children. Hong Kong children were 4.5 times more likely to have had a previous history of wheezing, and 8 times more likely to have had pneumonia than were Japanese children. Overall, 25.2% of the Hong Kong children versus 18.7% of the Japanese children had one or more of the surveyed chest illnesses, and their mean numbers of chest illnesses per sick child were 1.96 and 1.31, respectively. All of these differences were statistically significant, with the comparison of those with chest illnesses of borderline significance ($p = 0.066$).

We feel that the interpretation of these findings must be viewed in light of the degree of medical knowledge of the 2 populations. For a mother to report that she or her child had suffered from such diseases as bronchitis, pneumonia, asthma, tuberculosis, or allergic rhinitis, she would have had to have been told by a doctor of such a diagnosis/description of the problem. Because doctor-patient communication is poor in Hong Kong, and patients are frequently not told the diagnosis nor the names of the drugs that are prescribed, the knowledge/usage of

such medical terms among the population would be infrequent. This would be especially true among the working-class mothers whose average educational attainment is primary school only (11). Thus, these illnesses, which we have labeled as "respiratory diseases," would tend to be underreported in the Hong Kong population. On the other hand, such common descriptive terms as cough, phlegm expectoration, and wheezing are well understood by all, and thus the survey was able to reflect a more accurate recording of the prevalence of these symptoms.

Evidence for the fact that the greater unfamiliarity with medical terms among the Hong Kong mothers seemed to influence their reported frequencies is reflected in the unrealistically low reporting rate of tuberculosis. Only 1.6% of the Hong Kong versus 2.1% of the Japanese mothers reported having such a history. Yet it is known that the real rate should be much higher in Hong Kong since tuberculosis is still a common infectious disease in that community, with 137.4 new cases/100,000 population reported and a mortality rate of 8.4/100,000 (12) registered in 1983. The comparable incidence and mortality rates for Japan in 1985 were 48.4/100,000 and 3.9/100,000.

The Hong Kong subjects also reported more respiratory illnesses per person than did the Japanese subjects. These differences were especially notable among the children where the group mean values showed the Hong Kong children to be more than 2.9 times higher than those of the Japanese children (t test, p value = 0.001). No differences were observed in the frequencies of these illnesses by sex of the child.

Although the Hong Kong children were on average 8.5 months older than the Japanese children, we did not feel that this slight age difference could account for the large differences observed in the

Hong Kong children's higher reported frequencies of respiratory illnesses. In addition, the children in both populations have been immunized with the generally recommended schedule of diphtheria, pertussis, polio, BCG, etc. vaccines, so these differences were not due to immunization rates.

For both populations, however, there was a highly significant correlation between the frequency of respiratory illnesses of each mother and her child. Mothers who reported one or more illnesses for themselves were about twice as likely to report a similar number for their children.

For the Hong Kong mothers, a significant relationship was detected with increasing exposure to dust/smoke or gas/fumes in the workplace. The occurrence of respiratory illnesses seemed to be related to occupational exposures to such pollutants in 34% of those ever exposed to dust/smoke, and 46% of those ever exposed to gas/fumes. For the Hong Kong population as a whole, the attributable risk percentage was 10.0% for the former and 8.8% for the latter. However, analysis of the data by whether the mother was currently employed or not did not show any significant differences in the reported frequencies of respiratory illnesses for herself or her child.

The consistent tendency for Hong Kong subjects to have higher prevalence rates of respiratory illnesses than their Japanese counterparts is difficult to explain. Although, as shown above, some relationship was found with previous occupational exposure to dust or fumes in the workplace, the percentages of mothers currently working was not statistically different in the 2 groups.

The role of indoor air pollution in the home from passive smoking or heating/cooking activities has been investigated. Japanese fathers were about twice as likely to be smokers than were Hong Kong fathers. Moreover, in another report on the Hong Kong mothers (13), no association was found between the prevalence of chronic cough or sputum and the smoking patterns of their husbands. The etiologic role of cooking activities is also doubtful, as the proportion of kitchens with mechanical ventilation such as fans or cooking hoods was not different in Tokyo and Hong Kong. Previous case-control studies on the role of cooking fuels in lung cancer risk among females in Hong Kong (14) and Japan (15) did not find an association between fuel type (i.e., kerosene, liquid petroleum gas, charcoal, and wood grass) and lung cancer risk.

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Among the variables compared, Hong Kong families tended to be significantly larger, averaging 5.31 persons versus 4.54 for Japanese households. Among Hong Kong mothers, some association was found between larger household size and the frequency of respiratory illnesses, but such was not the case for household density. Moreover, larger household size was not associated with more respiratory illnesses among the Japanese mothers. Although both household size and density are related with socioeconomic status, the lack of an association with household density in Hong Kong would seem to indicate that these variables were not simply surrogate measures of household income. This is because, with the extremely expensive rental situation in Hong Kong, higher density living is directly associated with less income, whereas household size may reflect the persistence of an extended family system and, traditionally, according to the Confucian ethos, 3-generation families are desirable.

Several possibilities may help explain the patterns of respiratory illnesses in both populations. Recall bias may play a role as there was an increasing tendency for mothers reporting one or more respiratory illnesses for themselves to report the same for their children. This tendency was found in both the Japanese and the Hong Kong mothers, so it would not explain their highly different prevalence rates of respiratory illnesses. The principle of recall bias may have operated also on the finding that occupational exposures were related to respiratory illnesses among the Hong Kong mothers, since those with such illnesses may have been more likely to recall such past exposures than those without such problems. However, occupational exposures to such pollutants could only account for 9 to 10% of the respiratory illnesses in the Hong Kong mothers.

The role of cross infection, i.e., mother to child or other household members to mother or child, seems suggested by: (1) the direct association between household size and frequency of respiratory illnesses in the Hong Kong mothers, (2) the correlation between multiple respiratory illnesses within each mother-child pair in both populations, and (3) that Hong Kong families were significantly larger than Japanese families. However, no such association was found with household density, which would seem a more direct measurement of the potential for cross infection since the chances of spreading infectious respiratory diseases should be correlated with higher household densities. It appears that other not yet identi-

fied environmental factors are needed to explain these results.

The findings of this study, showing mothers and especially children in Hong Kong to have larger numbers of sick subjects and to have more illnesses per subject than their Japanese counterparts, are consistent with the findings of other surveys in both areas. Questions added to an international survey in 1986 on passive smoking and urinary cotinine levels sponsored by the International Agency for Research on Cancer indicated that women in Hong Kong were about 10 times more likely to report symptoms of chronic cough or phlegm than were women in Sendai, Japan. A population survey of respiratory illnesses in Japan in 1983 (T. Mori, personal communication) indicated that the reported age-adjusted rates of such illness for non-smoking women in Japan were similar to those reported among the Japanese mothers in this survey. Thus, we feel that the reported differences in the frequencies of respiratory illnesses in Hong Kong and Japan are not artifactual.

These results agree with the contrasting female lung cancer incidence rates in the 2 areas. The epidemiologic data showed that chronic bronchitis was associated with increased risk for lung cancer in females (1). Moreover, the multistage model of carcinogenesis makes this association biologically plausible since these symptoms result from and result in a chronic irritation effect on the respiratory tract, making it more susceptible to the action of carcinogenic initiators or promoters. Previous occupational exposure to dust or fumes was associated with respiratory illnesses in the Hong Kong mother, and frequencies of such illnesses in the mother were directly related to those in her child. Although this could account for a portion of the respiratory illnesses, more investigation is needed to find other etiologic agents in the Hong Kong environment to account for the higher frequency of respiratory health problems. A recent time-trend analysis by Barker and Osmond (16) in England and Wales showing that respiratory diseases in childhood led to higher mortality rates from chronic bronchitis and emphysema later in adult life, ominously suggests that the high rates of childhood respiratory illnesses found in the Hong Kong population today portends to excess mortality from respiratory diseases in the future when these children reach 40+ yr of age.

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Hole, D.J., Gillis, C.R., Chopra, C., Hawthorne, V.M. "Passive smoking and cardiorespiratory health in a general population in the west of Scotland" BMJ 299: 423-427, 1989.

ABSTRACT. Objective-To assess the risk of cardiorespiratory symptoms and mortality in non-smokers who were passively exposed to environmental smoke. Design- Prospective study of cohort from general population first screened between 1972 and 1976 and followed up for an average of 11.5 years, with linkage of data from participants in the same household. Setting- Renfrew and Paisley, adjacent burghs in urban west Scotland. Subjects- 15399 Men and women (80% of all those aged 45-64 resident in Renfrew or Paisley) comprised the original cohort; 7997 attended for multiphasic screening with a cohabitee. Passive smoking and control groups were defined on the basis of a lifelong non-smoking index case and whether the cohabitee had ever smoked or never smoked. Main outcome measure- Cardiorespiratory signs and symptoms and mortality. Results- Each of the cardiorespiratory symptoms examined produced relative risks > 1.0 (though none were significant) for passive smokers compared with controls. Adjusted forced expiratory volume in one second was significantly lower in passive smokers than controls. All cause mortality was higher in passive smokers than controls (rate ratio 1.27 (95% confidence interval 0.95 to 1.70)), as were all causes of death related to smoking (rate ratio 1.30 (0.91 to 1.85)) and mortality from lung cancer (rate ratio 2.41 (0.45 to 12.83)) and ischaemic heart disease (rate ratio 2.01 (1.21 to 3.35)). When passive smokers were divided into high and low exposure groups on the basis of the amount smoked by their cohabitees those highly exposed had higher rates of symptoms and death. Conclusion- Exposure to environmental tobacco smoke cannot be regarded as a safe involuntary habit.

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Passive smoking and cardiorespiratory health in a general population in the west of Scotland

David J Hole, Charles R Gillis, Carol Chopra, Victor M Hawthorne

Abstract

Objective—To assess the risk of cardiorespiratory symptoms and mortality in non-smokers who were passively exposed to environmental smoke.

Design—Prospective study of cohort from general population first screened between 1972 and 1976 and followed up for an average of 11.5 years, with linkage of data from participants in the same household.

Setting—Renfrew and Paisley, adjacent burghs in urban west Scotland.

Subjects—15 399 Men and women (80% of all those aged 45-64 resident in Renfrew or Paisley) comprised the original cohort; 7997 attended for multiphasic screening with a cohabitee. Passive smoking and control groups were defined on the basis of a lifelong non-smoking index case and whether the cohabitee had ever smoked or never smoked.

Main outcome measure—Cardiorespiratory signs and symptoms and mortality.

Results—Each of the cardiorespiratory symptoms examined produced relative risks >1.0 (though none were significant) for passive smokers compared with controls. Adjusted forced expiratory volume in one second was significantly lower in passive smokers than controls. All cause mortality was higher in passive smokers than controls (rate ratio 1.27 (95% confidence interval 0.95 to 1.70)), as were all causes of death related to smoking (rate ratio 1.30 (0.91 to 1.85)) and mortality from lung cancer (rate ratio 2.41 (0.45 to 12.83)) and ischaemic heart disease (rate ratio 2.01 (1.21 to 3.35)). When passive smokers were divided into high and low exposure groups on the basis of the amount smoked by their cohabitees those highly exposed had higher rates of symptoms and death.

Conclusion—Exposure to environmental tobacco smoke cannot be regarded as a safe involuntary habit.

of lung cancer; it overcomes many of these criticisms. The survey prospectively studied a general population aged 45-64 years, and the collected data allowed participants from the same household to be identified. The measure of exposure to environmental tobacco was obtained directly from cohabitees and did not rely on self reporting. Data on prevalences of symptoms of respiratory and cardiovascular disease, forced expiratory volume in one second, mortality, and incidence of cancer are all available for this population. The findings reported here update an earlier report; it adds 567 further deaths to the previous findings¹ and extends the range of baseline measurements to include forced expiratory volume in one second. Confounding variables such as social class, blood pressure, cholesterol concentration, body mass index, and social class have been allowed for in calculating relative risks for passive smokers.

Subjects and methods

This general population cohort comprises all men and women aged 45-64 years resident in the towns of Renfrew and Paisley in the west of Scotland between 1972 and 1976.¹ Eligibility was established by a door to door census of all households in the two towns. Everyone who met the age and residency criteria was invited to attend one of 12 temporary centres for a multiphasic cardiorespiratory screening examination.¹ Between 1972 and 1976, 15 399 residents (an 80% response) completed a standardised self administered questionnaire that included questions on smoking behaviour and was checked by experienced interviewers when subjects attended for screening. Respiratory symptoms were assessed with the Medical Research Council's bronchitis questionnaire. By identifying participants from the same household it was possible to study varying exposures to tobacco smoke in a subsample of 3960 men and 4037 women and to calculate relative risks for a range of cardiorespiratory variables including mortality.

Four groups, in which the index case was aged 45-64 at the time of the survey, were defined based on the index case and on the cohabitees ever or never having smoked.

(1) Control: the index case had never smoked and lived at the same address as another subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(2) Passive smoking: the index case had never smoked and lived at the same address as a subject who had.

(3) Single smoking: the index case was a smoker or ex-smoker and lived at the same address as a subject who had never smoked. No one else in the household who attended for screening was a smoker or ex-smoker.

(4) Double smoking: the index case was a smoker or ex-smoker who lived at the same address as a subject who was also a smoker or ex-smoker.

If the index cases were ex-smokers they were classified as single smokers or double smokers depending on whether the cohabitees had never smoked or

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Introduction

Though evidence has accumulated about the risk to health of involuntary, or passive, exposure to environmental tobacco smoke, further information is required from cohort studies to confirm these observations. Deleterious effects on the respiratory system of infants and children have been observed^{2,3} as have chronic effects on lung function in adults,^{4,5} but these findings have been criticised on methodological grounds.⁶ An overview of 10 case-control and three cohort studies estimated a relative risk of 1.35 for lung cancer in people passively exposed compared with non-exposed controls.⁶ Three studies have reported increased (though not significant) risks of ischaemic heart disease in non-smokers with partners who smoke.⁷⁻⁹ Problems in interpreting these findings include lack of an objective measure of dose or exposure, failure to adjust for confounding variables, inappropriate methods of statistical analysis, and failure to measure other potentially important variables.¹⁰

This report is based on the Renfrew-Paisley survey, which was carried out in an area with a high incidence

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ever smoked. If the cohabitants were ex-smokers the index cases were classified as passive smokers if they had never smoked or as double smokers if they had ever smoked. Thus the controls represent a group whose passive exposure was as low as possible within the constraints of the study design. Results for the two active smoking groups have been included to give some indication of dose-response and provide a perspective for any differences found between the control and passive smoking groups.

A cohabitee was defined as a respondent sharing the same household environment and examined at the same time in the survey as the index case. Some households contained cohabitants of the same sex. Some of the subjects who were examined were above or below the age range eligible for inclusion in the study. These subjects were not analysed as index cases but information on their smoking behaviour as cohabitants was used as the measure of passive exposure for eligible index cases.

Mortality data was obtained from the National Health Service central register and the General Register

TABLE 1—Composition of groups exposed to cigarette smoke

	No (%) of men (index cases)	No (%) of women (index cases)	Total
Controls (neither index case nor cohabitee ever smoked)	428 (100.0)	489 (12.1)	917
Passive smoking (only cohabitants ever smoked)	243 (6.1)	1795 (32.1)	1538
Single smoking (only index case ever smoked)	1420 (33.9)	331 (6.2)	1751
Double smoking (both index case and cohabitee ever smoked)	1869 (47.2)	1922 (47.6)	3791
Total	3960 (100)	4037 (100)	7997

TABLE 2—Social class of men in groups exposed to cigarette smoke. Figures in parentheses are percentages

Social class	Exposure group			
	Controls	Passive smoking	Single smoking	Double smoking
I	23 (5.4)	13 (5.3)	61 (4.3)	78 (4.2)
II	85 (19.9)	37 (15.2)	225 (15.8)	235 (12.4)
III non-manual	43 (10.2)	23 (9.5)	197 (13.9)	204 (10.9)
III manual	157 (36.2)	94 (39.5)	558 (37.9)	771 (41.3)
IV	86 (19.7)	59 (24.3)	315 (22.2)	438 (23.4)
V	17 (4.0)	11 (4.5)	68 (4.8)	122 (6.5)
Insufficient information	3 (0.7)	4 (1.6)	16 (1.1)	21 (1.1)
Total	428 (100.1)	243 (99.9)	1420 (100)	1869 (100)

TABLE 3—Smoking habits of cohabitants in passive smoking and double smoking groups. Figures are percentages (numbers)

No. of cigarettes smoked per day by cohabitee	Index case			
	Men		Women	
	Passive smoking group	Double smoking group	Passive smoking group	Double smoking group
1-14	31.3 (76)	30.4 (54.1)	15.1 (196)	11.4 (217)
15-24	46.1 (112)	53.7 (98.5)	41.6 (541)	54.1 (1060)
25-34	43.9 (102)	49.9 (89.8)	36.8 (599)	37.1 (713)
35-44	4.1 (10)	6.4 (12.7)	11.6 (143)	19.1 (36.7)
Ex-smoker	21.6 (53)	17.3 (32.3)	49.1 (638)	32.4 (625)

TABLE 4—Age and sex standardized rates of respiratory and cardiovascular symptoms related to exposure to cigarette smoke. Numbers of index cases with symptoms are given in parentheses

	Exposure group			
	Controls (n=917)	Passive smoking (n=1538)	Single smoking (n=1751)	Double smoking (n=3791)
Respiratory symptoms:				
Asthma	2.3 (22)	3.3 (44)	10.5 (189)	10.5 (394)
Chronic bronchitis	7.8 (72)	9.1 (122)	26.4 (451)	28.7 (1079)
Pneumonia	10.1 (95)	12.2 (167)	18.4 (329)	16.4 (618)
Dyspnoea	5.3 (48)	6.9 (91)	17.6 (327)	18.3 (681)
Cardiovascular symptoms:				
Angina	4.4 (43)	4.7 (64)	7.7 (140)	9.1 (334)
Myocardial infarction	1.6 (6)	1.1 (15)	1.4 (21)	1.5 (49)
Major abnormality found on electrocardiogram				
Mean forced expiratory time in one second (l)	2.32	2.31	2.12	2.09
Unadjusted	2.31	2.23	2.12	2.07

Office for Scotland. Incidence of cancer was obtained through the cancer registry system and used to verify that the classification on the death certificate was the same as that received by the registry. Data presented are complete to the end of December 1985, an average follow up of 11.5 years.

Prevalences for respiratory and cardiovascular symptoms were standardized for age and sex using the age and sex distribution of the whole cohort as standard. Similarly, mortality was standardized for age and sex using life tables to estimate survival at 11 years of follow up."

Mean forced expiratory volumes in one second for the four exposure groups were adjusted for age, height, and sex by determining the best fit set of parallel regression models for forced expiratory volume in one second as a linear function of age and height for men and women separately in each group. The mean and adjusted forced expiratory volume in one second for each group was then calculated for the average age and height of men and women separately, and a weighted average (corresponding to the proportion of men and women) was computed. Probability values were obtained from the analysis of variance.

Estimates of relative risk and 95% confidence intervals for passive smokers compared with controls were adjusted for age, sex, social class, diastolic blood pressure, serum cholesterol concentration and body mass index (weight (kg)/height (m)² × 100) using the logistic regression model¹¹ for cardiorespiratory symptoms and Cox's proportional hazards model for mortality.¹² Levels of significance were derived from the partial likelihood function.¹³ The biomedical data processing programs (BMDP) package was used to compute estimates of risk and levels of probability.¹⁴

A supplementary questionnaire in two of the 12 centres in which the survey was carried out asked subjects the extent to which they were exposed to cigarette smoke from any other person in the household, irrespective of whether these people were eligible for or attended the survey, and also in their work environment.

Results

The number of men and women in the four exposure groups is shown in table 1. Passive smokers comprised

TABLE V—Age and sex adjusted mortality per 10 000 per year by category of exposure to cigarette smoke. Figures in parentheses are actual numbers of deaths

	Controls (n=467)	Passive smoking (n=754)	Single smoking (n=430)	Double smoking (n=734)
All causes	83.1 (99)	97.4 (164)	140.0 (430)	135.4 (734)
Lung cancer	1.4 (2)	5.0 (7)	23.2 (54)	21.4 (93)
Ischaemic heart disease	27.3 (80)	47.7 (54)	61.0 (171)	46.7 (240)
All causes of death related to smoking	40.8 (71)	72.2 (104)	130.4 (342)	129.9 (592)

TABLE VI—Age adjusted prevalences of respiratory and cardiovascular symptoms and age standardised mortality per 10 000 per year for women in control and passive smoking groups. Figures in parentheses are numbers of actual cases

	Controls (n=467)	Low exposure (n=754)	High exposure (n=541)
Prevalence			
Respiratory symptoms:			
Infected sputum	2.1 (10)	2.4 (18)	3.1 (17)
Persistent sputum	6.4 (31)	5.0 (45)	8.4 (46)
Dyspnoea	12.7 (60)	11.2 (84)	16.2 (88)
Hypertension	4.1 (19)	3.4 (29)	5.7 (30)
Cardiovascular symptoms:			
Angina	3.4 (17)	4.1 (32)	5.8 (31)
Minor abnormality found on electrocardiogram	8.4 (2)	1.1 (2)	8.5 (2)
Mortality:			
Lung cancer	38.3 (31)	64.4 (70)	87.8 (54)
Lung cancer	3.2 (1)	2.5 (2)	5.7 (3)
Ischaemic heart disease	6.8 (3)	14.2 (14)	28.0 (16)
All causes of death related to smoking	34.9 (17)	35.2 (39)	47.3 (30)

6.1% (243/3960) of men and 32.1% (1295/4037) of women. Of the cohabitants, 91.6% (7325) were of the opposite sex. The composition of the groups by social class is shown in table II.

The extent of passive exposure experienced by passive smokers in relation to subjects in the double smoking group is shown in table III. In all, 46.1% (112) men and 41.8% (541) women in the passive smoking group lived in households where the cohabitee was smoking 15 or more cigarettes a day. This compared with 52.7% (985) men and 56.2% (1080) women in the double smoking group. Ex-smokers were more common in households in which the index case had never smoked.

The prevalence of signs and symptoms for the four exposure groups is shown in table IV. For each of the four respiratory measures (infected sputum, persistent sputum, dyspnoea and hypertension), the rates in the control group were lower than those in the passive smoking group and considerably lower than in the single and double smoking groups. The rates for angina and major abnormalities found on electrocardiography were similar in the control and passive smoking groups and lower than in the active smoking groups.

Mean forced expiratory volumes in one second adjusted for sex, age, and height were significantly higher ($p < 0.01$) in controls than in those passively

exposed to cigarette smoke and were significantly higher than among active smokers.

Mortality adjusted for age and sex in the four groups is presented in table V. Total mortality was higher among passive smokers than controls. This was reflected in the category of all causes of death related to smoking and was highest for ischaemic heart disease. Lung cancer mortality was higher among passive smokers than controls but the number of deaths involved was small.

The supplementary questionnaire on exposure to cigarette smoke at home and work allowed a check to be made of the smoking habits of other household members who were not part of the survey. A regular smoker living in the same household was reported by 5% (2/44) of controls compared with 69% (27/39) of passive smokers. Of women, 21% (13/62) of controls lived in households with a regular smoker compared with 63% (125/197) of passive smokers.

Women reported that most of their passive exposure was at home rather than at work, which suggested that they were the appropriate group in which to examine whether there was a dose-response relation. A high exposure passive smoking group was therefore defined as women whose cohabitee was smoking 15 or more cigarettes daily, and the remaining female passive smokers were defined as a low exposure group. Table VI presents the age standardised rates for respiratory and cardiovascular symptoms and mortality for the control and the low and high exposure passive smoking groups. For each of the four respiratory symptoms the highly exposed passive smokers had rates that were higher than those in passive smokers whose exposure was low and those in the controls. There were no consistent differences between the low passive exposure group and the controls. A similar pattern was found for angina but not for major abnormalities detected by electrocardiography.

The adjusted forced expiratory volume at one second was significantly lower in passive smokers with high exposure compared with those with low exposure (mean 1.43 ± 0.18 l; $p < 0.05$). No significant difference was found between passive smokers with low exposure and controls (1.89 ± 0.18 l). Age adjusted mortality was increased for the passive smokers with high exposure compared with low and with controls for all cause mortality, all cause mortality related to smoking, ischaemic heart disease, and lung cancer.

Table VII shows the adjusted relative risks for passive and active smokers compared with controls. For each variable the relative risk associated with passive smoking was > 1.0 . The confidence interval included 1.0 except for ischaemic heart disease, for which the estimated risk was significantly different from unity ($p = 0.008$).

Table VIII shows the relative risks for double smokers compared with single smokers after additional adjustment for quantity smoked. Dyspnoea was signifi-

TABLE VII—Relative risks associated with passive smoking adjusted for age, sex, and social class and for cardiovascular variables, diabetic blood pressure, serum cholesterol concentration, and body mass index

	Relative risk (passive smokers compared with controls)	95% Confidence interval	p Value	Relative risk (active smokers compared with controls)
Respiratory symptoms:				
Infected sputum	1.34	0.76 to 2.36	0.3	4.33
Persistent sputum	1.19	0.83 to 1.47	0.3	4.46
Dyspnoea	1.09	0.82 to 1.45	0.5	1.40
Hypertension	1.21	0.81 to 1.82	0.3	3.77
Cardiovascular symptoms:				
Angina	1.11	0.73 to 1.70	0.4	1.89
Major abnormalities found on electrocardiogram	1.27	0.48 to 3.35	0.4	1.51
Mortality:				
All causes	1.27	0.95 to 1.76	0.10	2.02
All causes of death related to smoking	1.30	0.91 to 1.85	0.15	3.13
Ischaemic heart disease	2.01	1.21 to 3.35	0.008	3.27
Lung cancer	2.41	0.43 to 12.10	0.3	10.44

TABLE VIII—Relative risks in double smokers compared with single smokers, adjusted for age, sex, amount smoked, and social class and for cardiovascular variables, diastolic blood pressure, serum cholesterol concentration, and body mass index

	Relative risk	95% Confidence interval	p Value
Respiratory symptoms:			
Infective sputum	0.96	0.79 to 1.16	0.65
Persistent sputum	1.06	0.92 to 1.21	0.45
Dyspnoea	1.25	1.05 to 1.49	0.02
Hypersecretion	1.02	0.87 to 1.20	0.75
Cardiovascular symptoms:			
Angina	1.17	0.95 to 1.44	0.15
Major abnormalities found on electrocardiogram	1.11	0.68 to 1.79	0.65
Mortality:			
All causes	1.01	0.87 to 1.18	0.9
All causes of death related to smoking	0.99	0.84 to 1.16	0.9
Ischaemic heart disease	0.89	0.72 to 1.11	0.3
Lung cancer	1.13	0.79 to 1.63	0.5

scantly more common among double smokers ($p=0.02$), and though none of the other variables was significant, six had risks >1.0 .

Discussion

Whether inhaling other people's tobacco smoke is a risk factor for lung cancer and other diseases related to smoking is now under serious scientific consideration. Studies of the concentrations of cotinine in the urine and saliva of passive smokers suggest that the dose received may be equivalent to smoking up to three cigarettes a day.²⁰ Though sidestream smoke contains different proportions of chemical constituents than does mainstream smoke and the same dose received passively might not translate directly to the same risk as in active smokers, the risks expected for passive smokers will probably be of a similar magnitude to those found in active smokers of up to three cigarettes daily; consequently, only very large studies will have sufficient power to detect such risks. A meta-analysis is currently the only way to establish precise estimates of risk, and it is essential that all studies are included.

This paper updates a previous publication¹¹ with mortality now extended to an average follow up time of 11.5 years and the control and passive smoking groups redefined to exclude those who smoked only pipes or cigars and those who smoked cigarettes irregularly. The original questionnaire in its coded form did not distinguish pipe and cigar smokers and those who smoked fewer than five cigarettes a day from non-smokers. Written information on the questionnaires allowed this to be clarified, and these additional data were added to the computer files.

The sample size in this study does not provide sufficient statistical power to detect risks of the magnitude expected. Thus the lack of significance should not be the sole criterion of whether a genuine effect may be present. Several findings should be borne in mind when interpreting these results. Firstly, for each of the 10 measures examined, from respiratory symptoms to causes of mortality, the relative risk was consistently larger than unity. This remained so after adjusting for intervening risk factors such as age, sex, social class, blood pressure, cholesterol concentration, and body mass index. Secondly, the one measure for which sufficient statistical power was available—that is, forced expiratory volume in one second—gave a significant result. Thirdly, when a group of passive smokers with high exposure was defined there was an increase in the dose-response relation for nine of the 10 variables. Fourthly, in comparison with the relative risks found for the two active smoking groups, each increased risk was biologically plausible, with the possible exception of that for ischaemic heart disease.

The findings for respiratory symptoms are similar to those of other studies: a decreased forced expiratory volume in one second in passive smokers has been

found previously,²¹ and the risks for liping cancer are consistent with those in the overview by Wald *et al.*⁶ Few data relate passive smoking to cardiovascular disease, but a relative risk as high as 2.2 for mortality from ischaemic heart disease in passive smokers has been quoted.⁷ Our risk of 2.0 seems large in comparison with that found for active smokers, and the possibility that chance has inflated this risk cannot be excluded, but as the lower 95% confidence limit for the relative risk is greater than one it would appear that chance alone is not responsible for the excess.

When investigating risks close to unity it is important to consider the effect of potential biases. Biases may operate at the time data are collected. Between 1972 and 1976, however, passive smoking was not an issue. Subjects reported their own smoking habits and no self-reporting of passive exposure was undertaken. It was not until 1983 that subjects within the same household were linked, and this was carried out without any reference to the measures of outcome examined subsequently.

There is no direct measure available to prove that the passive smokers received a higher environmental dose of tobacco smoke than the controls, but in the supplementary questionnaire that covered the smoking habits of household members irrespective of whether they attended the original survey only 5% of controls said that there was a current smoker in the household, compared with 63% of passive smokers. Greater exposure to tobacco smoke at work supported the idea that passive smokers were more likely than controls to be in contact with environmental tobacco smoke outside the home. This was measured by Wald and Ritchie,²² who showed that non-smoking husbands of smoking wives had higher urinary cotinine concentrations than non-smoking husbands of non-smoking wives. Our definition of categories of exposure is comparable with that of other studies and would seem to identify groups with different mean levels of passive exposure. The high level of heavy smoking in our cohort²³ might also indicate that this difference is greater than that found in other studies.

The problem of smokers deliberately classifying themselves as non-smokers²⁴ is a far less serious bias in cohort studies than in case-control studies, because at the interview stage there is no indication which subjects will subsequently die. The likelihood of differential misclassification rates—that is, higher in the passive smoking than in the control group—is debatable as this implies that someone in the double smoking group is more likely to pretend to be a non-smoker than someone in the single smoking group. When the cohabitee is a smoker the reverse may be more likely to be true.

It has been suggested that non-smokers who marry smokers may be different from non-smokers who marry non-smokers.²⁵ A higher proportion of passive smokers were in social classes III manual, IV, and V, but no differences were found for other possible risk factors such as occupation, raised blood pressure, cholesterol concentration, or body mass index. In any case the final analysis, which estimated the relative risks, adjusted for each of these factors.

The effect of passive smoking on those who already smoke is far harder to isolate. The dose received by active smokers from smoking ranges widely,²⁶ and adding a small extra component due to passive exposure may not lead to much of a difference in mean doses for double smokers compared with single smokers. Hence, the increased risk for double smokers relative to single smokers may be substantially less than that for passive smokers relative to controls. The statistical power of a single study is an important consideration and in the absence of other published data on this aspect it is difficult to interpret our results

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for the effects of passive smoking on smokers. Therefore the main emphasis of this paper is an estimation of the risks of passive smoking in lifelong non-smokers; data are presented for the active smoking groups to provide an estimate of dose-response.

Our results are based on a general population cohort study carried out in an area with a high level of diseases related to smoking. A consistent increase in risk was observed in passive smokers for each of the 10 variables measured covering respiratory symptoms, forced expiratory volume in one second, cardiovascular symptoms, and subsequent mortality, including lung cancer and ischaemic heart disease. A dose-response relation was seen, and the risks were biologically plausible in relation to the size of the risks found for the active smokers. These three factors taken together increase our concern that exposure to other people's tobacco smoke cannot be regarded as a safe involuntary practice.

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Carbohydrate deficient transferrin: a marker for alcohol abuse

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Abstract

Objective—To assess the value of serum carbohydrate deficient transferrin as detected by isoelectric focusing on agarose as an indicator of alcohol abuse.

Design—Coded analysis of serum samples taken from patients with carefully defined alcohol intake both with and without liver disease. Comparison of carbohydrate deficient transferrin with standard laboratory tests for alcohol abuse.

Setting—A teaching hospital unit with an interest in general medicine and liver disease.

Patients—22 "Self confessed" alcoholics admitting to a daily alcohol intake of at least 80 g for a minimum of three weeks; 15 of the 22 self confessed alcoholics admitted to hospital for alcohol withdrawal; 68 patients with alcoholic liver disease confirmed by biopsy attending outpatient clinics and claiming to be drinking less than 50 g alcohol daily; 47 patients with non-alcoholic liver disorders confirmed by biopsy; and 38 patients with disorders other than of the liver and no evidence of excessive alcohol consumption.

Intervention—Serial studies performed on the 15 patients undergoing alcohol withdrawal in hospital.

Main outcome measure—Determination of relative value of techniques for detecting alcohol abuse.

Results—Carbohydrate deficient transferrin was detected in 19 of the 22 (86%) self confessed alcohol abusers, none of the 47 patients with non-alcoholic

liver disease, and one of the 38 (3%) controls. Withdrawal of alcohol led to the disappearance of carbohydrate deficient transferrin at a variable rate, though in some subjects it remained detectable for up to 15 days. Carbohydrate deficient transferrin was considerably superior to the currently available conventional markers for alcohol abuse.

Conclusion—As the technique is fairly simple, sensitive, and inexpensive we suggest that it may be valuable in detecting alcohol abuse.

Introduction

The medical and social consequences of alcohol abuse are major problems throughout the world. Although many people readily acknowledge the extent of their alcohol consumption, others attempt to conceal it, and we lack reliable objective means of identifying surreptitious alcohol consumption. Currently available laboratory markers have considerable limitations, being insensitive, non-specific, or dependent on liver damage. The mean corpuscular volume rises in patients with thyroid disease, folic acid deficiency, and liver disease,¹ whereas serum γ -glutamyltransferase activity is affected by drugs that induce microsomal enzymes as well as rising in all forms of obstructive liver damage.² Serum aspartate aminotransferase activity is more commonly raised in alcoholics than alanine aminotransferase activity is, and whereas a ratio of aspartate to alanine aminotransferase activity of greater than 2:1 is strongly suggestive of alcoholic liver disease³ this is of little value in subjects in whom the

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Koo, L.C., Ho, J.H.C., Ho, C., Matsuki, H., Shimizu, H., Mori, T., Tominaga, S. "Personal Exposure to Nitrogen Dioxide and Its Association with Respiratory Illness in Hong Kong" Am Rev Respir Dis 141: 1119-1126, 1990.

SUMMARY: In 1985, 362 primary schoolchildren and their 319 mothers were surveyed in Hong Kong to study the possible relationship of air pollution to respiratory illnesses. Using nitrogen dioxide (NO₂) measured by personal samplers as a measure of air pollution, the study aimed to identify the major sources of NO₂ in the indoor environment and see whether its increased presence was associated with respiratory symptoms. The levels of NO₂ among the mothers was found to increase by 21% if dust exposure was reported from the workplace, 18% if they used such cooking fuels as liquid petroleum gas or kerosene, 11% when kitchens did not have ventilating fans, and 10% when incense was burned at home. In terms of respiratory symptoms, an increase in NO₂ levels of 19% was reported among those with allergic rhinitis and 18% among those with chronic cough. The levels of NO₂ among children were correlated with levels measured in classrooms, all of which had opened windows so that the NO₂ came from outdoors. No association was found between children's NO₂ levels and respiratory symptoms. With the exception of smoking by the father and the children's NO₂ levels, no association was found between smoking at home and NO₂ levels.

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Personal Exposure to Nitrogen Dioxide and Its Association with Respiratory Illness in Hong Kong¹⁻³

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Introduction

Studies on respiratory illness among children in the United Kingdom (1-3) and the United States (4) have found it to be associated with exposure to nitrogen dioxide (NO₂), especially in homes where gas instead of electricity is used for cooking. Exposure to NO₂ has also been found to be associated with lower pulmonary function among children (4). In addition, ambient levels of oxides of sulfur and nitrogen have been correlated with higher rates of chronic cough and phlegm among women in six communities in Japan (5). These data are supported by animal experiments which have shown that mice exposed to NO₂ have higher rates of respiratory infections and lowered ability to clear viable bacteria from the lung (6).

However, epidemiologic data on the effects of NO₂ on respiratory illnesses and pulmonary function are inconsistent (7), with some studies showing no relationship between NO₂ and respiratory illnesses (8-10), or between levels of air pollutants and the results of lung function tests (2,6). The conflicting results on the relationship of air pollution with respiratory illnesses may be partially due to: (1) studies that measured NO₂ levels did so by spot measurements of the ambient levels in kitchens, bedrooms, living rooms, or outdoor air and not by cumulative personal exposure levels, and (2) the problems of confounding by other sources of air pollutants such as active or passive smoking, cooking fumes, or air pollutants in the workplace.

To explore the possibility that NO₂, a measure of air pollution from combustion, might be related to the high rates of chronic bronchitis among children and mothers in Hong Kong (11), a study was conducted in 1985 in which personal exposure to NO₂ was measured by a badge worn by each subject, and data on respiratory symptoms and indoor sources of combustion were obtained through questionnaires.

SUMMARY In 1985, 362 primary schoolchildren and their 319 mothers were surveyed in Hong Kong to study the possible relationship of air pollution to respiratory illnesses. Using nitrogen dioxide (NO₂) measured by personal samplers as a measure of air pollution, the study aimed to identify the major sources of NO₂ in the indoor environment and see whether its increased presence was associated with respiratory symptoms. The levels of NO₂ among the mothers was found to increase by 21% if dust exposure was reported from the workplace, 18% if they used such cooking fuels as liquid petroleum gas or kerosene, 11% when kitchens did not have ventilating fans, and 10% when incense was burned at home. In terms of respiratory symptoms, an increase in NO₂ levels of 19% was reported among those with allergic rhinitis and 18% among those with chronic cough. The levels of NO₂ among children were correlated with levels measured in classrooms, all of which had opened windows so that the NO₂ came from outdoors. No association was found between children's NO₂ levels and respiratory symptoms. With the exception of smoking by the father and the children's NO₂ levels, no association was found between smoking at home and NO₂ levels.

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Methods

From May 20 to 29, 1985, children attending a coeducational primary school in the Kwun Tong district of Hong Kong were contacted for this study. The school was selected, in cooperation with the local government's Department of Education, to represent subjects from a working class background in an industrial neighborhood of metropolitan Hong Kong. The sample included 390 students in Grades 2 to 6 attending 11 classes in the school. Through the children, the mothers were also asked to cooperate in this study. The response rate was 100% cooperation from the children and 97% from their mothers/guardians. To limit this analysis to mothers and children with complete data sets, the following were excluded from the initial subjects who were contacted: 10 guardians who did not return the questionnaire, 15 guardians who were not related as mother to the child, three mothers who did not return the NO₂ badge, and the redundancy of 43 mothers who had replied more than once because two or more of their children had been included in the survey. Thus, our final sample size for analysis consisted of 319 mothers, with a mean age of 37.9 (SD = 5.6), and their 362 children, with a mean age of 10.0 (SD = 1.5).

A modified version of the questionnaires on respiratory illnesses developed by the British Medical Research Council's Committee on the Aetiology of Chronic Bronchitis (12) and the American Thoracic Society's Division of Lung Disease (13) was used. In the self-completed questionnaire, all subjects were

asked whether they had experienced allergic rhinitis, asthma, pneumonia, or chronic cough or phlegm lasting for 3 months or more and unrelated to a cold or flu infection. In addition, the version for the children asked about the occurrence of wheezing and whether they had a runny nose lasting more than 6 months. The version for the mothers included questions on bronchitis, tuberculosis, and other chest diseases. Questionnaires concerning the children were answered by their mothers.

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TABLE 1
NO₂ LEVELS BY AGE AND SEX IN HONG KONG SCHOOLCHILDREN*

Age (yr)	Boys		Girls		Boys + Girls	
	(n)	Mean NO ₂ (ppb)	(n)	Mean NO ₂ (ppb)	(n)	Mean NO ₂ (ppb)
7	8	14.14	8	15.45	14	14.71
8	34	15.67	26	15.45	60	15.58
9	21	21.56	34	21.44	55	21.48
10	48	20.18	46	22.17	94	21.15
11	29	22.03	28	24.23	57	23.11
12	36	18.19	35	18.23	71	18.21
13	7	13.34	4	12.49	11	13.03
Total	183	18.48	179	19.77	362	19.12

* Boys versus girls, *t* test *p* values: for age, *p* = 0.92; for NO₂, adjusted for age, *p* = 0.22.

TABLE 2
NO₂ LEVELS BY AGE IN HONG KONG MOTHERS:

Age (yr)	Number	Mean NO ₂ (ppb)
30 or below	18	21.22
31-35	101	18.87
36-40	124	19.06
41-45	39	20.72
46-50	29	20.27
50 or older	8	17.28
Total	319	19.39

In order to obtain data on indoor sources of air pollution, there were questions on smoking habits of family members, types of heating and cooking fuels, frequency of cooking, ventilation patterns, burning of incense and mosquito coils, and the mother's exposure to dust or fumes in the workplace.

All subjects were asked to wear a badge-type personal sampler pinned to their outer clothing at the upper chest level for 24-h exposure. At bedtime, or when bathing, subjects were instructed to put the badge face-up on an adjacent table so that contact with ambient air was continuous. The badge, measuring 50 × 40 × 7 mm and weighing 15 g, allows for NO₂ to diffuse through five layers of hydrophobic fiber filters before being absorbed on a sheet of triethanolamine solution. The concentration of NO₂ in the sampler was determined by adding a color reagent to the soaked filter and measuring the absorbance of the diazo compound by a spectrophotometer (14). The sensitivity of this sampler is as much as 124.8 µg/h/m³ (66 ppb/h) and has a reported accuracy of ± 20% (15).

Badges (*n* = 48) were also hung in the classrooms and playground area in the school so that comparisons could be made between ambient indoor and outdoor levels and the personal exposure levels of the children. All classrooms in the six-story school had opened windows for ventilation since the mean outdoor temperature was 27°C and the humidity was 81% during the 2 wk of data collection.

Statistical analyses were conducted by the use of the SPSS-X computer package. The statistical significance of the relationship between different degrees of exposure to sources

of air pollution and NO₂ levels was performed using Student's *t* test, if the data were exact, and the ANOVA *F*-test when the data were categorical. Tests for linear trend for understanding possible dose-response relationships were done by the *F*-test for linearity (16). Analysis of the correlation between children's and mothers' NO₂ levels, and their relationship to classroom and playground levels, was done using the Pearson's coefficient of correlation, with the *p* value obtained from the one-sample *t*-test (16). Stepwise regression coefficients were calculated to determine the contribution of independent sources of indoor air pollution to the cumulative personal exposure levels of NO₂.

Results

The children's NO₂ levels by age and sex are shown in table 1. The higher NO₂ levels among those 9 to 11 yr of age was apparently due to the sampling procedure used during the 2 wk. Children in this age bracket were in Grades 3 to 5, and they were sampled during the first week when the mean ambient level was 21.4 ppb, whereas those in Grades 2 and 6 were sampled the following week when the mean ambient level was 17.8 ppb. These observations are supported by the finding that the mean NO₂ values for all children sampled in the first week was 21.9 ppb versus 16.2 ppb for those sampled in the second week. Because the classes were coeducational, there was no statistically significant difference in age between boys and girls, and there was no difference by sex in their NO₂ levels when matched for class or adjusted by age.

The age distribution and NO₂ levels among the mothers in table 2 show no relationship with age. Analysis by which week the mothers were sampled showed them to have patterns opposite from that of the children. Mothers in the first week had an average level of 17.5 ppb NO₂ versus 21.8 ppb for those in the second week. Generally, the average level of 19.4 ppb for all mothers was not statistically differ-

ent (*p* = 0.89) from that of 19.1 ppb among their children by paired *t* test analysis. The mothers' NO₂ badges were exposed 1 day after that of their children so that week of exposure did not affect these results.

When comparing ambient with personal NO₂ levels exposed on the same days, the children's levels were highly correlated with classroom measurements (*r* = 0.75, *p* = 0.004). Similarly, classroom levels of NO₂, which were on floors 2 to 5, were correlated with playground levels on the ground floor (*r* = 0.80, *p* = 0.03). But correlation of the children's NO₂ levels with playground levels (*r* = 0.79, *p* = 0.18) was high but statistically not significant, showing that they spent less time there. If the playground levels are taken as a surrogate measure of outdoor levels on the ground level, the NO₂ levels for the mothers were not associated with the playground levels (*r* = 0.12, *p* = 0.46).

In analyzing the correlation coefficient of the mothers' NO₂ with that of their daughters, sons, or all children combined, there was no significant correlation between levels in mothers and that of their children. Although it is possible that boys would tend to spend more time playing outdoors and girls more time playing and helping their mothers at home, there was no difference between the girls and boys in terms of their NO₂ levels and correlation with NO₂ levels in the classrooms or playground.

Environmental Tobacco Smoke

As a result of recent interest in the possible role of environmental tobacco smoke (ETS) as a contributor to NO₂ levels, table 3 shows the levels of NO₂ among children and mothers by the smoking habits of family members. To gather more specific measurements of exposure, the questionnaire asked about the average number of cigarettes smoked at home by family members, and the hours of direct exposure by the child or mother to this smoke. As can be seen, there was no relationship between the child's or mother's NO₂ levels and the number of cigarettes smoked by the father/husband, mother/self, mother + father/mother + spouse, or total number of family smokers per day. Although not shown, there was also no association between their NO₂ levels and the hours they were exposed to cigarette smoke at home or in the workplace.

Stepwise regression analysis of the various independent variables measuring

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TABLE 3
FAMILY SMOKING HABITS AND NO₂ LEVELS

	Children		Mothers	
	(n)	NO ₂ (ppb)	(n)	NO ₂ (ppb)
Cigarettes smoked by father/husband at home per day, n				
0	233	18.87	201	19.59
1-5	68	18.26	63	19.02
6-10	38	20.65	33	19.55
11+	18	20.60	17	18.25
Trend p value	0.15		0.61	
Cigarettes smoked by mother/self at home per day, n				
0	357	19.14	314	19.40
1-5	4	18.45	4	21.33
6+	1	14.47	1	7.68
Trend p value	0.57		0.74	
Cigarettes smoked by father + mother/mother + spouse at home per day, n				
0	232	18.85	200	19.61
1-5	68	18.43	63	18.91
6-10	36	20.60	31	19.84
11+	21	20.24	20	18.17
Trend p value	0.17		0.62	
Total smokers in the family, n				
0	218	19.00	191	19.77
1	123	19.72	113	19.17
2	16	17.58	12	15.79
3+	5	14.41	3	17.73
Trend p value	0.41		0.16	

TABLE 4
STEPWISE REGRESSION COEFFICIENTS OF CIGARETTE SMOKE
AND NO₂ LEVELS AMONG MOTHERS AND CHILDREN

Independent Variable	NO ₂ Levels	t Test: p Value
Mothers' NO ₂ levels		
Smokers at home, n	-0.714	0.36
Cig/day mother smokes at home, n	-0.488	0.39
Hours mother exposed to smoking at home	-0.100	0.19
	p = 0.22	
Never-smoked mothers' NO ₂ levels		
Smokers at home, n	-0.977	0.23
Hours mother exposed to smoking at home	-0.106	0.17
	p = 0.13	
Children's NO ₂ levels		
Smokers at home, n	-0.775	0.26
Hours child exposed to smoking at home	-0.147	0.61
Cig/day father smokes at home, n	0.205	0.02
Cig/day mother smokes at home, n	-0.220	0.61
	p = 0.21	

levels of smoking in the home is shown in table 4. It is interesting to note that increased smoking generally led to *reduced* levels of NO₂ among mothers and children. The only exception was data on the number of cigarettes smoked by the father per day in which each cigarette smoked contributed to an average increase of 0.2 ppb of NO₂ in the exposed child. This exception, coupled with the fact that NO₂ levels were not higher among five mothers who were currently smoking at the time of the survey, seems to indicate that other factors were affecting this relationship.

The overall tendency for NO₂ levels to decrease as the number of smokers or cigarettes smoked in the home increased might be due to compensation behavior. That is, as family members smoked and polluted the air at home, increasing measures of ventilation would be taken by the mother, such as opening windows, turning on fans, etc. The exception of father's cigarettes on children's NO₂ levels may have arisen because they were less concerned with opening windows and reducing smoke inhalation by their children. Because the wife's NO₂ level was found to decrease as her husband smoked

more at home, this seems to indicate that the children's exposure to the father's tobacco smoke occurred when the mother was not in the same room and in a position to increase ventilation. As this study was done in 1985, before publicity and public awareness of the possible health hazards of environmental tobacco smoke, these findings seem consistent with the expected behaviors of Chinese parents. Smoking among primary school children is also rare in Hong Kong, so the effects of active smoking by children was probably negligible on these results.

Cooking and Heating Habits

The most common types of fuel used for cooking and heating water were bottled liquid petroleum gas (LPG), piped gas, and kerosene. None of the surveyed households had electric stoves because electricity is a more expensive source of energy and its lack of immediate heat control makes it less conducive for Chinese cooking. Although LPG and piped gas were the major sources of fuel used in the kitchen, it was also common for some households to use the cheaper but smellier kerosene stoves as a supplemental source of energy for cooking or room heating.

It can be seen in table 5 that the children's NO₂ levels were not affected by the type of fuel used in the home. This probably reflected the tendency for children to spend little time in kitchens, which were usually very small (25 ft²) and frequently just a makeshift corner of a balcony. Among mothers, however, NO₂ levels were highest for LPG and kerosene users and lowest for those with piped gas, and these findings were statistically significant. The greatest difference of 3.8 ppb was found between those who used only piped gas and those who did not (p value < 0.001).

To estimate the mother's exposure to combustion during cooking, table 6 shows her NO₂ levels by the frequency she cooked meals or fried food per day in the presence or absence of mechanical ventilation in the kitchen. Ventilation was defined as the use of a mechanical fan in a fume hood or on a window to disperse fumes from the kitchen to outdoors. Because the Chinese style of frying generates large amounts of smoke and oil fumes, most households (79%) used them, and the NO₂ levels of mothers in kitchens with such types of mechanical ventilation were significantly lower than those without by an average of 2.3 ppb. It can also be seen that if ventila-

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TABLE 5
TYPES OF HOUSEHOLD COOKING AND HEATING FUELS AND NO₂ LEVELS

	LPG Only		(LPG + Kerosene) Only		Kerosene Only		Piped Gas Only	
	Yes	No	Yes	No	Yes	No	Yes	No
Children								
Exposed, n	148	214	69	293	27	335	113	249
Mean NO ₂ , ppb	19.53	18.84	19.18	19.11	17.66	19.24	19.14	19.11
t test p value	0.31		0.95		0.21		0.97	
Mothers								
Exposed, n	127	192	62	257	24	295	102	217
Mean NO ₂ , ppb	20.52	18.64	21.36	18.91	19.43	19.38	18.84	20.59
t test p value	0.04		0.09		0.97		0.000	

Definition of abbreviation: LPG = liquid petroleum gas.

TABLE 6
EFFECT OF FREQUENCY OF COOKING AND VENTILATION ON MOTHERS' NO₂ LEVELS

	Ventilation during Cooking*				All (NO ₂ , ppb)
	Yes		No		
	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)	
All kitchens	253	18.90	66	21.24	19.39
t test p value	0.01				
Meals cooked per day, n					
0	6	19.06	13	20.13	19.79
1	36	17.76	3	21.51	18.05
2	122	18.70	23	21.44	19.13
3	89	19.64	27	21.58	20.09
Trend p value	0.30		0.54		0.34
Meals where food is fried per day, n					
0	11	19.05	12	19.55	19.31
1	150	18.56	28	21.32	18.99
2	78	19.26	22	21.70	19.80
3	14	20.48	4	23.27	21.08
Trend p value	0.43		0.30		0.31

* Fume hood or ventilating fan used in kitchen.

tion was present, the mother's NO₂ levels were not noticeably increased if she cooked more meals or fried food more often per day. However, among mothers without ventilated kitchens, there was a trend toward increasing NO₂ with more frequent frying, although this was not statistically significant.

Because piped gas and mechanical ventilation are likely to be present together, table 7 shows the effects of both variables

on NO₂ levels. Eighty-seven percent of the households with piped gas had ventilation fans, whereas this was apparent in only 76% of those who used other types of fuel. The presence of ventilation fans especially lowered NO₂ levels among households without piped gas.

In an analysis of children's cooking activities with NO₂ levels, which took into account the greater participation of girls (21%) than of boys (10%), there was no

TABLE 7
EFFECTS OF VENTILATION AND PIPED GAS ON MOTHERS' NO₂ LEVELS

	Ventilation during Cooking*				t Test p Value
	Yes		No		
	(n)	(NO ₂ ppb)	(n)	(NO ₂ ppb)	
Piped gas used					
Yes	89	16.77	13	17.26	0.82
No	164	20.06	53	22.22	0.05
t test p value		0.01		0.002	

* Fume hood or ventilating fan used in kitchen.

association between cooking activities, the presence of ventilating fans, and NO₂ levels, as shown in table 8.

Burning of Incense or Mosquito Coils

Because about half of the households in Hong Kong burn incense daily for religious reasons, and one-eighth burned mosquito coils in the summer period, the questionnaire asked whether these items had been burned in the previous 24 h to coincide with the sampling of personal NO₂ levels. It can be seen in table 9 that the children's NO₂ levels were unaffected by such sources of burning, but among the mothers, those who did burn incense had higher NO₂ levels by 1.9 ppb than those who did not (p = 0.04).

Workplace Exposures

To assess the contribution of workplace exposures to the mothers' NO₂ levels, table 10 shows that their NO₂ levels increased as self reports of exposure to occupational dust increased in severity. For those who reported high levels of such exposure, their NO₂ levels were 4.0 ppb higher. However, such a trend was not found for exposure to fumes or gases in the workplace. In a subtropical climate such as that in Hong Kong where high heat and humidity encourages quick decomposition of organic matter, the sources for some of the fumes and gases could have come from rotting food and moldy growths. Noncombustible chemicals used in the electronics industry, which is a major employer of these women, could have also contributed to the reports on fumes.

Respiratory Symptoms and NO₂ Levels

The mean NO₂ levels among those reporting the presence or absence of nine different respiratory symptoms is shown in table 11. Among the 312 mothers who had never smoked, those reporting to have allergic rhinitis had a mean NO₂ level of 22.6 ppb versus 19.0 ppb among those who did not, and the t test p value was 0.002. An increase in NO₂ levels was also associated among mothers reporting positively for chronic cough, as they had NO₂ measurements of 22.5 ppb versus 19.1 ppb among those without (p value = 0.05). Among the children, there were no statistically significant differences in NO₂ levels by presence versus absence of the respiratory symptoms.

To assess the association of multiple respiratory symptoms to NO₂ levels, table

TABLE 8
EFFECTS OF VENTILATION AND COOKING ON CHILDREN'S NO₂ LEVELS

	Ventilation during Cooking				t Test p Value	All (NO ₂ , ppb)
	Yes		No			
	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)		
Boys help cook						
Yes	14	20.17	5	16.96	0.39	19.33
No	130	18.74	34	17.01	0.17	18.38
t test p value		0.38		0.99		0.52
Girls help cook						
Yes	30	18.81	9	21.66	0.29	19.47
No	112	19.74	28	20.31	0.69	19.66
t test p value		0.50		0.60		0.75

TABLE 9
EXPOSURE* TO INCENSE OR MOSQUITO
COILS AND NO₂ LEVELS

	Incense Burned at Home		Mosquito Coil Burned at Home	
	Yes	No	Yes	No
	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)
Children				
Exposed, n	177	185	52	310
Mean NO ₂ , ppb	19.57	18.69	18.73	19.19
t test p value		0.19		0.63
Mothers				
Exposed, n	154	165	43	276
Mean NO ₂ , ppb	20.36	18.48	19.69	19.34
t test p value		0.04		0.79

* Incense or mosquito coils were burned during the 24 h that the NO₂ badges were worn.

12 shows that there was no dose-response effect among the children, but there was a significant trend ($p = 0.01$) among mothers who had never smoked. Mothers who had four or more of the following symptoms: chronic cough, chronic sputum, asthma, pneumonia, allergic rhinitis, tuberculosis, or bronchitis, had NO₂ levels that were 5.7 ppb higher than those who had none.

The indoor sources of combustion that were previously evaluated and had statis-

tically significant associations with levels of NO₂ among mothers are summarized in table 13.

Discussion

This study of 319 mothers and their 362 children attending a primary school in the Kwan Tong district of Hong Kong had three aims: (1) identify indoor sources of combustion in working class households, (2) assess their possible contribution to levels of NO₂ as measured

TABLE 12
MULTIPLE RESPIRATORY SYMPTOMS
PER SUBJECT AND NO₂ LEVELS

Respiratory Symptoms (n)	Children*		Never-smoked Mothers†	
	(n)	Mean NO ₂ (ppb)	(n)	Mean NO ₂ (ppb)
0	244	19.26	230	18.83
1	61	18.70	52	19.92
2	25	17.59	19	22.95
3	12	21.52	7	21.79
≥ 4	9	19.15	4	24.57
Trend p value		0.92		0.01

* The presence of the following, apart from those caused by colds/flu: allergic rhinitis, asthma, chronic cough, chronic sputum, pneumonia, runny nose, and wheeze. Data from one child was deleted because it was incomplete.

† The presence of the following, apart from those caused by colds/flu: allergic rhinitis, asthma, bronchitis, chronic cough, chronic sputum, pneumonia, and tuberculosis.

by personal passive samplers, and (3) examine whether higher NO₂ levels were associated with self reports of respiratory symptoms.

The major sources of combustion in Hong Kong homes were fires from cooking food, heating water, burning religious incense and mosquito coils, and the smoke from cigarettes. Outdoor sources of NO₂ came from motor vehicles, factories, restaurants, incinerators, aircraft, etc. Because the children's NO₂ levels were significantly correlated with ambient levels, and were less affected by home sources of combustion, these data suggest that most of their NO₂ came from outdoor sources. By contrast, their mothers NO₂ levels were dependent on their indoor activities. If they had piped gas and mechanical ventilation in the kitchen, their levels of NO₂ were reduced by 18 and 11%, respectively. But their NO₂ levels increased by 10% if incense was burned at home, and by 21% if they reported high

TABLE 10
OCCUPATIONAL EXPOSURE TO GAS OR
FUMES AND NO₂ LEVELS AMONG
HONG KONG MOTHERS

Exposure	Number	Mean NO ₂ (ppb)
Dust		
None	248	18.83
Low	40	19.51
High	31	22.92
F-test p value*		0.04
Fumes		
None	282	19.56
Low	24	18.16
High	13	17.97
F-test p value*		0.59

* One-way ANOVA F-test among groups with different exposures.

TABLE 11
RESPIRATORY SYMPTOMS AND NO₂ LEVELS

Symptom	Children			t Test p Value	Never-smoked Mothers			t Test p Value
	Yes		No		Yes		No	
	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)	(n)	(NO ₂ , ppb)
Allergic rhinitis	33	18.75	329	19.16	37	22.62	275	18.97
Asthma	29	20.07	333	19.04	4	20.60	308	19.39
Bronchitis	—	—	—	—	24	21.56	288	19.22
Chronic cough*	52	19.12	309	19.12	25	22.50	287	19.13
Chronic sputum*	41	17.53	321	19.32	30	20.47	282	19.29
Pneumonia	28	19.91	334	19.05	3	21.68	309	19.38
Runny nose†	13	17.16	349	19.19	—	—	—	—
Tuberculosis	—	—	—	—	5	19.43	307	19.40
Wheeze	34	20.07	326	19.02	—	—	—	—

* Symptoms reported apart from those associated with colds/flu for children, and lasting > 3 months for mothers.

† Mucoid or purulent discharge from the nose > 6 months.

TABLE 13
SUMMARY FACTORS ASSOCIATED WITH NO₂ LEVELS IN MOTHERS

Factor	Yes versus No Difference in NO ₂ Levels		t-Test p Value
	(ppb)	(%) ^a	
Dust at work, high versus none	3.99	21.1	0.01
Use piped gas for cooking	-3.75	-18.2	0.000
Mechanical ventilation in kitchen	-2.34	-11.0	0.02
Burn incense at home	1.88	10.1	0.04

^a (Yes NO₂ ppb minus No NO₂ ppb) divided by Yes NO₂ ppb.

levels of dust at work. However, despite their different sources of NO₂, the mean levels of NO₂ between mothers and children were not significantly different, whether in paired or group analysis.

These results were dependent on the NO₂ badges being properly exposed, and on mothers being able to give an accurate account of their exposure to sources of combustion and experiences with respiratory illnesses. The children were instructed on how to use the badges, and attached and removed them from their clothing under the guidance of field workers to minimize mishandling. Although there are always problems of inaccurate reporting in self-completed questionnaires, because the mothers' NO₂ levels were found to increase as their exposure to fires in the home increased, this indicated that the data based on NO₂ badges and recall were generally accurate. Yet it is also possible this is a result of bias. Mothers more conscientious in reporting exposure to combustion and respiratory illnesses might have exposed their NO₂ badges for longer periods of time or placed them more closely to sources of combustion. We tried to minimize this problem by not informing the mothers what the badge was measuring.

When the Hong Kong NO₂ exposure levels were compared with those from other studies that used a similar type of NO₂ personal badge monitoring system, the level for Hong Kong subjects at 19 ppb was moderately low. A study of volunteers from 3 Asian cities in February 1983 found NO₂ levels among subjects from Bangkok to be 12 ppb, Manila 14 ppb, and Tokyo 36 ppb (17). Another study conducted from January to February 1982 in Tokyo recorded mean NO₂ levels of 36 ppb among primary school-children (18) and 47 ppb among their mothers (19).

These data indicate that climatic factors heavily influence indoor levels of NO₂. The study by Mori and coworkers (17) showed that in temperate zone cli-

mates such as that in Japan, where home heating and insulation reduces the dispersion of air pollutants from indoor sources of combustion, indoor levels of NO₂ at 48 ppb in the winter were twice as high as outdoor levels at 21 ppb. By comparison, in tropical climates such as those in Bangkok and Manila, indoor levels of NO₂ at 10 and 13 ppb, respectively, were lower than the outdoor levels of 13 and 14 ppb.

Hong Kong's situation is similar to that of Bangkok and Manila in being a semi-tropical climate, so windows are kept open throughout the year and there is little accumulation of air pollutants from home-generated sources. However, unlike Bangkok and Manila, outdoor levels of NO₂ may not be simply higher than indoor levels in Hong Kong. This is because most of the Hong Kong subjects reside, study, and work in multistory buildings, which are less common in these other cities, and outdoor levels of NO₂ were found to decrease with increasing height of a building. In our survey of the school, the following mean levels were measured at the following heights: ground-floor playground, 25 ppb; second-floor classrooms, 19 ppb; third-floor classrooms, 21 ppb; fourth-floor classrooms, 20 ppb; and fifth-floor classrooms, 19 ppb. Another study of ambient NO₂ levels by the Hong Kong Government's Environmental Protection Agency (20) found that the ratio of ground to twelfth floor levels was 1.46 (i.e., 38 to 26 $\mu\text{g}/\text{m}^3$). For the Hong Kong mothers, the average home was located on the twelfth floor of a building so that, generally, NO₂ levels were likely to be lower indoors than outdoors if no combustion was taking place in the home. This factor also reduces the possibility that the higher NO₂ levels among mothers with allergic rhinitis or chronic cough was simply due to their greater tendency to stay indoors.

When we analyzed data on ETS and NO₂, the mothers' NO₂ levels were unaffected by their own or other people's

smoking habits at home or in the workplace. However, we only had five mothers who claimed to be currently smoking. Another international study on ETS and urinary cotinine/creatinine ratios (21), which included 102 Hong Kong women who claimed to be nonsmokers, one-fourth of whom were mothers in this study, indicated that one Hong Kong subject had ratios above 100 ng/mg, and six had ratios above 50 ng/mg. Thus, the possibility of deception on smoking habits varied from 1 to 6%, and would be too small to influence the NO₂ levels.

The children's NO₂ levels increased with the number of cigarettes their fathers smoked at home, but they were unaffected by hours of exposure at home, the number of cigarettes smoked by their mothers, or the number of smokers at home. This general lack of an effect of active or passive smoking on NO₂ levels was also found by Matsuki and coworkers (22) in their study of primary school children and mothers in Japan.

Our results also point to some of the advantages and disadvantages of measuring NO₂ by passive personal samplers. The NO₂ data reflected personal cumulative exposures over the 24-h period sampled, and thus is an improvement over previous studies (3, 4, 8) in which monitoring machines were placed in fixed positions in kitchens, living rooms, or bedrooms in the home. The latter method provides indirect measures of personal exposure since people do not stay in one position or in one room over a daily or weekly period. On the other hand, we were unable to account for high peaks of NO₂ exposure, which may reach up to 1 ppm (4) when gas stoves are turned on for cooking. This may help explain why respiratory symptoms were not associated with NO₂ levels in children, but were found for allergic rhinitis and chronic cough in mothers. The children's levels reflected a continuous exposure to moderate background levels of NO₂ since they had little direct contact with fires. Their mothers, however, were exposed to acute high levels of NO₂ when burning occurred in the home, and low background levels at other times. These short-term, acute exposures to high levels of NO₂ might trigger allergic rhinitis symptoms in the mothers because NO₂ is a respiratory irritant (23). The symptoms of chronic cough in mothers might also have been a result of long-term exposure to NO₂, which the children had not had.

In comparing our results on respiratory symptoms with findings from other

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studies, our data agree with those found by Keller and coworkers (8), Melia and colleagues (3), and Ware and coworkers (10) in that respiratory illnesses in children were not associated with their exposure levels to NO_2 . Our study was also able to assess personal levels of NO_2 exposure, which is an improvement over other studies that based NO_2 levels on the type of cooking stove in the home (24).

The comparability of our data with others is also complicated by the fact that Chinese cooking styles differ from those in the West. Foods are usually stir-fried over high heat for a short time, and the subsequent production of oil and smoky fumes almost necessitates good ventilation in the kitchen. By contrast, cooking in the West is commonly done by turning on the oven for hours at a time. Therefore, the total duration of combustion is shorter, resulting in lower NO_2 levels in Hong Kong households. Moreover, no one used the kitchen stoves for home heating or clothes drying. Thus, our overall levels of NO_2 may be lower than in other studies done in temperate-zone climates. This seems supported by the fact that the Hong Kong mothers' mean NO_2 level of 19 ppb was less than half that of the 47 ppb measured for Japanese mothers (19).

The inconsistent findings in the literature may also be affected by lack of emphasis on the role of ventilation in homes. In our data, the use of ventilating fans reduced NO_2 levels significantly, especially in the presence of more polluting types of fuel such as liquid petroleum gas and kerosene. Thus, the assumption that a gas stove will increase personal exposures to NO_2 needs more refinement. A similar situation was suggested by our data on environmental tobacco smoke. Increasing levels of smoking at home tended to decrease NO_2 levels, possibly because as the indoor air was polluted by smoking, more measures were taken to ventilate the room.

Our study did find that among mothers with no history of smoking, NO_2 levels were higher by 3.4 ppb among those with chronic cough, and by 3.7 ppb among those with allergic rhinitis. The association of NO_2 with cough and phlegm (5) and allergic rhinitis (25) was also found in two Japanese studies even though both used outdoor measurements of NO_2 . Moreover, a study of nonsmokers in Maryland found such symptoms associated with gas stoves (26).

The possible link between NO_2 and respiratory symptoms in nonsmoking

adults is further supported by our finding of a dose-response relationship ($p = 0.01$) between NO_2 levels and the number of respiratory symptoms reported by mothers. Mothers with four or more symptoms had mean NO_2 levels 30.5% higher than did those with none. Because the NO_2 exposure measurements were unknown to the respondents, these correlations suggest that the association is not due to recall bias and support the possibility that long-term chronic exposures to NO_2 , or an associated by-product of combustion, may be deleterious to the respiratory health of adult nonsmokers.

The biologic mechanisms for such an effect are difficult to explain since most of the published research is based on very high exposure levels. Studies on rats have shown morphologic changes in their lungs after NO_2 exposures of 25 ppm or more. At lower and continuous exposures of 2 ppm of NO_2 , only slight destruction of the rat's bronchiolar epithelium and loss of cilia was noted, and these slight changes did not affect their survival or progress to fatal lung disease (23). In human occupational exposures, it is known that there is a delay of 3 to 30 h before the onset of respiratory symptoms, and concentrations of NO_2 need to reach 60 ppm for throat irritation and 100 ppm for cough (27). It is doubtful that such high exposures to NO_2 were encountered in Hong Kong homes. Yet the long-term health effects of low levels of exposure to NO_2 , possibly resulting in chronic obstructive bronchitis or emphysema in humans, are still uncertain.

In our previous report (11), we discussed the possibility that respiratory diseases such as allergic rhinitis, asthma, bronchitis, pneumonia, or tuberculosis were more likely to be underreported than were respiratory symptoms such as cough, phlegm, and wheezing. This is because the former are labels generally given by a doctor, and the latter are labels used by the lay public. In this population, knowledge of medical terms is limited because doctor-patient communication is poor. The recall of respiratory illnesses, however, was quite homogenous among these subjects since our previous report (11) showed that the frequency of reported respiratory illnesses did not vary with household density, i.e., number of persons per room, which is an indicator of socioeconomic status. This suggests that the observed associations between NO_2 levels and respiratory symptoms are not explained by a tendency of mothers with higher socioeconomic status to be more

likely to report symptoms and more conscientious about exposing NO_2 badges. It seems more likely that underreporting of respiratory diseases in this population reduced the possibility of finding a dose-response effect of NO_2 .

It is also possible that other factors such as diet may confound the relationship between respiratory symptoms and NO_2 levels. In a previous study on Hong Kong Chinese women who had never smoked, those with symptoms of chronic cough and phlegm were more likely to consume cured meats and alcohol and less likely to consume vegetables, fresh fruit, and milk (28, 29). Although it is speculative, it would seem possible that in some communities in the West, gas cooking could be associated with the higher risk diet since it is more likely to be found in older and therefore poorer homes than those with electric stoves. Certainly in Hong Kong, electric stoves were introduced about 5 yr ago, and they are installed only in the most expensive "luxury" housing units.

In conclusion, these results indicate that in a cross-sectional study of a community, measuring personal exposures to NO_2 allowed us to identify important sources of it, evaluate the effects of mechanical ventilation, and discriminate adults at higher risk for respiratory illnesses from home or workplace exposures. However, the usefulness of NO_2 as an indicator of air pollution may be limited in studying the health effects of ETS since the respirable particulate matter from ETS seems to be more important for health than gases such as nitrogen oxides (30). On the other hand, measuring NO_2 can validate reports of exposure to air pollutants coming from other sources of combustion. In our study, women who reported high levels of dust in the workplace also had increased levels of NO_2 , suggesting that some of the dust was generated from combustion. However, since NO_2 is only one by-product of combustion, it is possible that other unmeasured, but correlated, by-products of combustion, e.g., particulates, carbon monoxide, polycyclic aromatic hydrocarbons, etc., may be responsible for the health effects attributed to NO_2 in this study.

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ETS AND ADULT LUNG FUNCTION

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LUNG FUNCTION IN ADULTS

The studies that have investigated lung function in adults and its possible relationship to environmental tobacco smoke exposure are presented in this section. To aid in the interpretation of this literature, definitions of the major lung function parameters are provided below.

Df: One of the most widely used measures of pulmonary function in adults and children is forced vital capacity and is represented in the literature as FVC. This term refers to the maximum volume of gas that a person can expire as forcefully and rapidly as possible from their lungs immediately following a maximal inspiration of air. When a person's ability to expire air forcefully and rapidly from their lungs (FVC) is compromised, this can possibly be an indication of chronic obstructive lung disease. Decreased FVC is common in restrictive diseases such as pulmonary fibrosis and in obstructive diseases such as emphysema and asthma.

Df: A second important measure of pulmonary function is the forced expiratory volume in one second, which is abbreviated as FEV1 in the literature. The FEV1 measure is simply the amount of air that is expired in the first second of the FVC maneuver. As with FVC, this parameter is useful in the assessment of airway obstruction. The two parameters, FVC and FEV1, are often used in a ratio to determine the percentage of a person's FVC that is expired in the first second of the maneuver. A FEV1/FVC ratio lower than 65% to 70% is characteristic of obstructive lung disease. On the other hand, subjects with restrictive lung disease will often show a normal or exaggerated FEV1/FVC value.

Df: Forced expiratory flow, known as FEF25%-75%, is the average rate of flow of air during the middle half of an FEV maneuver. The FEF25%-75% is indicative of the status of the medium and small sized airways. Decreased values of FEF25%-75% are common in the early stages of obstructive lung disease. Low values of FEF25%-75% in combination with normal values of FVC and FEV1 are often indicative of early small airways abnormality. Reduced FEF25%-75% are sometimes seen in cases of severe restrictive disease as well.

All of these measures share a common problem: accurate assessment requires the full cooperation and maximal effort of the subjects under investigation. Accurate measures are sometimes

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therefore difficult to obtain. The studies are not consistent in the lung function parameters they measure, and there is also a lack of consistency among the results of the same function tests across studies. Following is a presentation of the major studies that have examined these lung function parameters in adults. The investigators who have found associations between impaired lung function and ETS exposure are often uncertain of the clinical meanings of the small decreases observed in their studies. Therefore, it is not suprising that no definitive conclusions have been reached regarding ETS exposure and its possible association with lung function in adults.

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RESULTS OF SELECTED STUDIES: ETS AND ADULT LUNG FUNCTION

Bouhuys, et al., 1978

The authors reported no associations between smoking in the home and increased symptoms or lung function loss among nonsmokers living in the same households.

Shephard, et al., 1979

The authors raise the possibility that subjective reporting of symptoms could have been "suggested" by the odor of the cigarette smoke.

White, et al., 1980

This study has received numerous criticisms.

Comstock, et al., 1981

Passive smoking in the home was not associated with the prevalence of respiratory symptoms and was only "suggestively associated" with impaired ventilatory function.

Kauffmann, et al., 1983

Opposite trends in FEV1 and FEF25-75 were found in men passively exposed to tobacco smoke, and the differences observed in women were slight and not statistically significant.

Jones, et al., 1983

The use of cooking fuels was found to be associated with impaired ventilatory function in a group of nonsmoking women.

Kentner, et al., 1984

Passive inhalation of tobacco smoke at home or the workplace was found not to be associated with impaired lung function in healthy nonsmokers.

Lebowitz, et al., 1985

Reported no direct association between ETS and lung function parameters in adult nonsmokers.

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Hosein, et al., 1986

The use of gas stoves was found to be associated with impaired lung function in women. It was reported that passive smoking in households where gas stoves were used appeared to have no effect on lung function values.

Masi, et al., 1988

The authors concede that their use of multiple tests of significance (involving both exposure and response measurements) are likely to have resulted in some associations achieving statistical significance by chance.

Kalandidi, et al., 1990

Assessment of exposure was based solely on the husband's smoking habit in terms of amount (daily), amount (total), and duration.

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Bouhuys, A., Beck, G.J., Schoenberg, J.B. "Do present levels of air pollution outdoors affect respiratory health?" Nature 276: 466-471, 1978.

SUMMARY: A sensitive lung function test does not show differences due to air pollution between lifetime residents in a rural area and those in a small industrial town in Connecticut. Also, there is no evidence that higher air pollutant concentrations elsewhere have any marked effects on the lungs. Severe pollution is dangerous and must be avoided, but at present, air pollution control outdoors does not deserve priority as a means of preventing chronic lung diseases.

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Do present levels of air pollution outdoors affect respiratory health?

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A sensitive lung function test does not show differences due to air pollution between lifetime residents in a rural area and those in a small industrial town in Connecticut. Also, there is no evidence that higher air pollutant concentrations elsewhere have any marked effects on the lungs. Severe pollution is dangerous and must be avoided, but at present, air pollution control outdoors does not deserve priority as a means of preventing chronic lung diseases.

WE have assessed the impact of urban residence on respiratory health in the population of an industrial US town, in comparison with a rural population which included lifetime dwellers as well as migrants who had previously lived in cities. We determined differences in respiratory health between these populations from (1) the prevalence of common respiratory symptoms, and of bronchitis and asthma, and (2) lung function tests which reflect airway calibre. As air pollution outdoors is one 'urban factor' which may affect the health of people living in cities, we monitored several air pollutants at different sites in both towns.

The urban area had a record of high air pollution (by US standards) in the recent past, but the urban-rural pollution contrast at the time of our study was modest. We therefore also compared our results with data on people living in more severely polluted urban areas, and in other rural areas, so as to expand the pollution contrast.

To assess respiratory health in both towns, we used a questionnaire and a sensitive, standardised lung function test. We studied children and adults of both sexes, and healthy persons as well as those with respiratory symptoms or disease. Our population samples were large and representative of the total population of both areas. In analysing the results, we took into account sex, race, age, body height, body weight, smoking habits, occupation and previous residence. We believe that this is the first report of a study which combines all these features, and that it allows more reliable conclusions concerning urban factors and chronic respiratory disease (other than lung cancer) than do previous studies.

Populations and air pollution

The urban site, Ansonia, Connecticut, is an industrial town where mean annual particulate concentrations were among the highest measured in Connecticut during 1966-72 ($188-152 \mu\text{g m}^{-3}$; ref. 1); high SO_2 concentrations (by US standards) were probably also common in the past. In 1973, particulate concentrations were lower but still significantly higher than at the contrasting rural site, Lebanon, Connecticut. Lebanon is a sparsely populated town without factories or major highways, away from cities. Outdoor pollutants (Table 1) were monitored in both towns for more than 1 yr, including the period of our population surveys^{1,2}. Concentrations of total suspended particulates (TSP, high-volume samplers) and of nitrogen dioxide were significantly higher at the urban sites, as were nitrates and sulphates (data in refs 1, 2). There were no significant differences for sulphur dioxide and ozone.

In two geographically defined areas (the town of Lebanon and the 4th Ward of Ansonia), we attempted to study all residents aged ≥ 7 yr. Response rates varied from 91-96% among boys and girls (7-14 yr) in both towns to 56% and 80% among 25-64-yr-old adults in Ansonia and Lebanon, respectively. From a private census and interviews of nonresponders³, we concluded that the responders adequately represent the total populations. There were only 20 black residents of Lebanon; our main analyses are therefore limited to the white residents of Lebanon and Ansonia (Table 2). Of the Lebanon subjects, 41% had previously lived in urban areas, possible selection factors made it important to consider these subjects separately from lifetime rural (LR) dwellers. The few 'previous rural' (PR) Ansonia residents were excluded from analysis. Three smoking categories were considered: lifetime nonsmokers, ex-smokers of cigarettes, and current cigarette smokers (Table 2).

Questionnaire

We used an extended version of the MRC bronchitis questionnaire (for text, see ref. 4). Questions were prompted by computer and read by trained interviewers; answers were recorded in computer memory. There has thus been no omission or loss of data. Detailed written instruction and supervision of interviewers by the investigators promoted consistency in the interviews. We were unable to allocate subjects at random to interviewers, but an examination of symptom prevalences by interviewer showed that interviewer variation had no important effects on our results. Previous urban (PU) and lifetime rural residents of Lebanon were seen by the same interviewers; interviewer variation can be excluded as a cause of differences between these groups.

Chronic bronchitis

First, we examined the symptom complex of chronic bronchitis (usual cough and phlegm, more than 3 months per year for ≥ 2 yr). In groups of men and women by age (25+ yr) and smoking habits, smokers always had higher prevalences than

nonsmokers or ex-smokers, but urban-rural differences were absent in all groups. For example, 19.0% of the rural male adult current smokers had chronic bronchitis, compared with 17.0% of their urban counterparts. Among both urban and rural residents aged ≥ 45 yr, the prevalence of chronic bronchitis was less than half that found (with identical methods) among active and retired textile workers at risk from occupational cotton dust exposure⁴.

Asthma

A history of bronchial asthma ('yes' to the question: 'have you ever had bronchial asthma?') was more common among rural than among urban residents, regardless of age. The difference was highly significant for males (6.7% in 1,142 rural (=LR+PU) males; 2.6% in 458 urban males; $\chi^2=9.99$, $P<0.01$) and similar differences, although not significant, persisted when only lifetime urban and rural residents were compared and when smoking was excluded by comparing only nonsmokers. Smoking habits were not significantly related to a history of bronchial asthma (χ^2 analysis).

Cough, phlegm and other symptoms

Chronic bronchitis may be an insensitive index of urban-rural differences because it is uncommon among nonsmokers. For its component symptoms, as well as wheezing and dyspnoea, we examined the relative importance of the residence variable and of sex, age and smoking habits in a weighted-least-squares analysis⁵ of all data in 15-64-yr-old nonsmokers and current smokers. We omitted children, because few of them had any symptoms, and the elderly, because they were too few in number. We also excluded ex-smokers; their symptom prevalences were usually close to those of nonsmokers. Table 3 summarises the best-fitting models. Cigarette smoking was the only variable consistently associated with increased prevalence of all symptoms, at $P<0.001$. For usual cough and phlegm, a linear residence variable (that is, $\text{LU}>\text{PU}>\text{LR}$) was highly significant among nonsmokers but not among smokers. The linear residence variable for dyspnoea was complicated by interactions between sex and smoking and between LU residence and smoking. The association between residence and dyspnoea was most pronounced among nonsmoking women (that is, 12.8% in 211 LR compared with 19.2% in 151 LU women). Among nonsmokers (men and women), LR residents had the lowest dyspnoea prevalence, among smoking men and

Table 1 The two towns and their air quality

	Lebanon (Rural)	Ansonia (Urban)
No. of inhabitants	3,800	21,200
No. of inhabitants per km^2	29	1,178
No. of dwellings per km^2	12	248
No. of vehicles per km^2	26	650
No. of commercial buildings and factories per km^2	0.03	17.8
Sulphur dioxide ($\mu\text{g m}^{-3}$)	10.4 ± 1.6 (41)	13.5 ± 1.7 (50)
Total suspended particulates ($\mu\text{g m}^{-3}$)	39.5 ± 4.2 (44)	63.1 ± 3.7 (50)
Nitrogen dioxide ($\mu\text{g m}^{-3}$)	55.5 ± 6.1 (41)	87.8 ± 4.9 (50)
Ozone ($\mu\text{g m}^{-3}$)	84.7 ± 4.4 (28)	88.5 ± 3.3 (35)

Demographic and geographical data from 1970 US Census, US Geological Survey maps, and municipal registries. Air pollutant data were obtained at 3-5 sites in Lebanon and at 4 sites in Ansonia, from January to December 1973, and are means \pm s.e.m. of 24-h average concentrations, except for ozone values, which are means \pm s.e.m. of peak 1-h concentrations (no. of observations in parentheses). Pollutant measurements (for methods and details, see refs 1, 2) were made with supervised, accurately calibrated samplers placed 120 cm above ground level, at least 16 m from any road and at least 11 m from physical obstructions (such as homes, trees). TSP and NO_2 were significantly ($P<0.001$) higher in Ansonia than in Lebanon, SO_2 and O_3 did not differ significantly.

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Table 2 Population groups by sex, age, residence and smoking habits

Residence	Age (yr)					Smoking			Total
	7-14	15-24	25-44	45-64	65+	NS	XS	S	
Males									
Lifetime rural (LR)	232	116	152	96	18	342	122	150	614
Previous urban (PU)	117	49	135	72	20	165	90	138	393
Lifetime urban (LU)	81	81	71	74	17	144	77	103	324
Previous rural (PR)	2	6	9	10	5	14	9	9	32
Totals	432	252	367	252	60	665	298	400	1,363
Females									
Lifetime rural (LR)	228	133	195	107	23	456	85	145	686
Previous urban (PU)	112	84	200	95	21	274	78	160	512
Lifetime urban (LU)	101	96	95	136	26	275	59	120	454
Previous rural (PR)	4	6	13	14	4	29	7	5	41
Totals	445	319	503	352	74	1,034	229	430	1,693

LR, lifetime residence in Lebanon and other rural areas; PU, current Lebanon rural resident but past residence in urban areas; LU and PR, lifetime urban and previous rural residents of Ansonia. Total number of subjects (3,056) represents the total studied (3,387) minus 331 excluded for one or more of three reasons: (1) smokers of pipes or cigars only; (2) 1 yr or longer work in dusty occupations (mines, quarries, foundries, potteries, cotton mills, asbestos factories); (3) unclear history of previous residence (urban or rural). Lifetime nonsmokers (NS) had never smoked tobacco in any form; additional smoking of pipes or cigars by ex-smokers (XS) or current cigarette smokers (S) was not considered. Among children (7-14 yr) the number of ex-smokers and smokers was too small for analysis.

women the PU residents had the highest prevalence (30.8% compared with 21.5% in both LR and LU residents). Residence effects were less significant or absent for wheezing, and they were complicated by interactions with age. The significant age variables in Table 3 reflect higher prevalences among older than younger subjects, except for usual cough, where the 25-44-yr-olds had more symptoms than those who were younger or older. Sex was significant for usual phlegm, being more common among men; and for dyspnoea, which was more prevalent among women.

Figure 1 shows the observed prevalences of usual phlegm in relation to all variables which contribute significantly to its prevalence. There are no interactions, and the fit of the model is the best of all five in Table 3. Observed prevalences among women are similar to those predicted by the model. Among young urban male nonsmokers, the model seems to overpredict prevalence, but the difference between actual and predicted prevalence is not significant. All smokers, regardless of residence, have a higher prevalence of usual phlegm than do LU nonsmokers.

Lung function

We selected the maximum expiratory flow volume (MEFV) curve as a simple, sensitive and comprehensive lung function test⁶. It provides information on lung volume (forced expiratory vital capacity, FVC) as well as maximum expiratory flow rates. In previous studies, maximum flow at mid-vital capacity (MEF 50%) detected airway-constrictor effects of cigarette smoke⁷, textile dust⁸ and air pollutants⁹ better than did measurements such as peak flow or forced expiratory volume in 1 s (FEV₁)¹⁰. We recorded MEFV curves on-line with a computer¹¹, calibrated every 2 h with a standard curve delivered by a mechanical device¹¹. From data on healthy lifetime nonsmokers (by race, sex and age group) in three US communities, including Lebanon and Ansonia, we have derived regression equations for FVC, FEV₁, the FEV₁/FVC ratio, peak expiratory flow rate (PEF) and maximum flow rates at two other points on the MEFV curve (MEF50% and MEF25%), as a function of age, height and weight¹². In the present study, these equations served to account for effects of age, height and weight in comparisons of lung

Table 3 Weighted least squares analysis of symptom prevalences

Symptom	Variables				Interactions			Fit of model	
	Smoking	Residence	Age	Sex	Age with:	Smoking with:	LU residence with:	P	% Variation explained
Cough	+++	+++*	++	0	Sex +++			0.714	74.8
Phlegm	+++	+++*	+	+++				0.998	81.1
Recent wheeze	+++	+	+	0	Smoking ++		Age +	0.759	79.7
Frequent wheeze	+++	0	0	0	Residence ++			0.962	67.4
Dyspnoea 1+	+++	+++‡	++	+++		Sex ++	Smoking +++	0.910	77.7

The table includes variables and interactions which contributed significantly to the explanation of the variation in symptom prevalence among all lifetime nonsmokers (NS) and current smokers (S) in Lebanon and Ansonia (age 15-64 yr). Logistic models always gave a better fit than did additive models. If x is the proportion of subjects with symptoms, the logistic model uses a logarithmic transformation of x , that is, $\ln [x/(1-x)]$, as the sum of effects of smoking, residence, age, sex and their interaction. Definition of symptoms: Cough and phlegm on most days for at least 3 months per year; recent wheeze, wheeze within past 12 months; frequent wheeze, wheeze at least a few times each week; dyspnoea 1+, dyspnoea when hurrying on level ground or walking uphill, or worse. Significance of variables and interactions: +++, $P \leq 0.001$; ++, $0.001 < P \leq 0.01$; +, $0.01 < P \leq 0.05$; 0, not significant. Explanation of interactions: Age \times sex: difference between sexes (M $>$ F) increases with age. Age \times smoking: age increase of prevalence greater for NS than S. Age \times residence: 25-64-yr-old PU residents more wheeze than LR and LU; 15-24-yr-olds lower prevalence regardless of residence. Smoking \times sex: less effect of smoking in females than males; NS females have relatively high prevalence. LU residence \times age: effect of residence on prevalence increase more pronounced in 25-44-yr-olds than in 15-24- and 45-64-yr-olds. LU residence \times smoking: LU smokers have lower prevalence than LR and PU smokers; LU nonsmokers have higher prevalence than LR and PU nonsmokers.

* Linear residence variable significant within NS only.

† LR < PU = LU, $P = 0.045$.

‡ Linear residence variable significant for NS and S.

function between groups of subjects. These comparisons were based on calculations of lung function residuals, that is, the differences between observed and predicted values of each measurement.

Analysis of variance of lung function residuals (Fig. 2) among LR, PU and LU residents by sex, age and smoking habits showed no significant differences for any of the measurements. LR, PU and LU nonsmokers had similar residuals, none of which differed significantly from zero or from each other. Smoking adults, on the other hand, had significantly more negative residuals than comparable nonsmokers, regardless of residence. Inclusion of adults with occupational exposure hazards (see legend to Table 1 for definitions) gave results similar to those in the population which excluded these persons.

Susceptible groups

Urban air pollution might not affect all residents, but only unusually sensitive groups within the urban population. Our data suggest that, if such groups exist, they cannot be readily identified on the basis of age (in those aged ≥ 7 yr), sex, race or smoking habits. Attempts to identify susceptible subgroups from questionnaire data were equally unsuccessful. Among smokers, the amount smoked seemed to be the main variable, affecting both symptom prevalence and lung function (unpublished observations), and there were too few nonsmoking urban (LU) residents who reported a history of asthma to allow a comparison of the severity of asthma among urban and rural residents. Among residents with usual cough and phlegm, lung function losses were minimal and not significant either among rural (LR) or urban (LU) residents. Thus, although there may be small groups of persons sensitive to factors in the urban environment that do not affect most people, we have not been able to identify them.

The 'urban factor'

Studies in several US cities¹³ have linked excess chronic bronchitis among smokers and nonsmokers to sulphur oxide and particulate pollution. In contrast, we have found that only lesser degrees of certain symptoms, not the composite syndrome of chronic bronchitis, may be associated with urban air pollution, and that this association only occurs in nonsmoking adults (age 15-64 yr; Table 3, Fig. 1). Among smokers, the influence of smoking overrides any differences associated with residence. However, the differences in symptom prevalences between urban and rural nonsmokers are not accompanied by differences in lung function. Even flows on MEFV curves (MEF50%; MEF25%), which are sensitive indices of airway obstruction¹⁴, did not differ. Thus, we have no objective evidence for substantial differences in respiratory health between urban and rural residents.

In the absence of lung function changes, what meaning should be attributed to the higher symptom prevalences among urban and previous urban nonsmokers? They might be due to trivial variables such as a different perception of questions by city and country people. The greater prevalence of dyspnoea among urban (LU) than rural (LR) nonsmoking women might be related to body weight (on average 4.1 kg more in 25-64-yr-old LU women than LR women). However, the LU-PU-LR gradient in prevalence of cough and phlegm among nonsmokers might reflect slight differences in respiratory health. For example, hypersecretion of bronchial mucus (leading to cough and phlegm production) may be more common among urban than rural nonsmokers. This disorder need not lead to progressive lung function loss¹⁵. It may be part of an adaptive mechanism (for example, increased mucus production may aid the clearance of pollutants) or it might represent incipient illness. Sputum from people in a polluted urban area may contain increased numbers of phagocytes and white cells¹⁶; these might secrete proteolytic enzymes which damage alveolar tissue¹⁷, or they may protect lung tissue against inhaled particles, or both. No firm conclusion is possible, but the lack of function loss among our older symptomatic, lifetime nonsmoking urbanites suggests

Table 4 Lung function in nonsmoking California and Connecticut residents

	Los Angeles	San Diego	Connecticut		
			LU	PU	LR
O ₂ (µg m ⁻³)	~300	~150	~100	~100	~100
TSP (µg m ⁻³)	124	78	65	42	42
No. subjects	90	135	73	41	56
Height (cm)	162	163	158	157	160
FEV _{1.0} (l)	2.44	2.43	2.10	2.08	2.25
MEF50% (ls ⁻¹)	3.38	3.37	2.96	2.81	3.09

Data for white, female, lifetime nonsmokers aged 45-64 yr. Los Angeles and San Diego data from Cohen *et al.*¹⁸. Data for males are similar. Higher lung function values in nonsmoking California women are explained by their height. All function values are close to those predicted for healthy nonsmoking adult white females¹⁹.

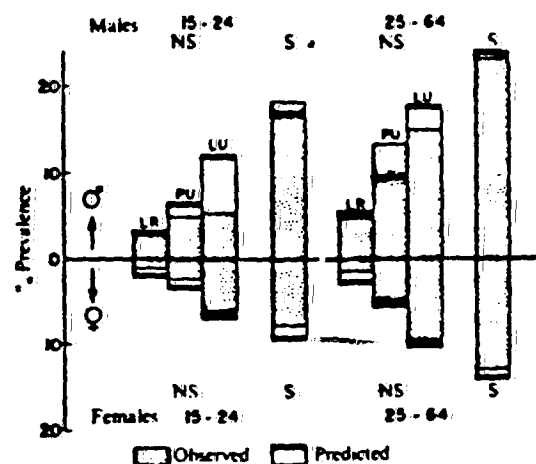
that the increased symptom prevalences are not associated with significant long-term deleterious effects on the lungs. Nor does our study indicate additive or synergistic effects between air pollution and smoking: lung function loss among smokers was similarly regardless of residence.

Our study cannot distinguish between air pollution and other urban factors as possible causes of the increased symptom prevalences among PU and LU nonsmokers. However, in a study designed to detect effects of air pollution peaks on daily symptoms among women in high- and low-pollution areas near Rotterdam, Wever¹⁸ found significant associations, mostly in nonsmokers, of pollution peaks with cough, phlegm and dyspnoea, but rarely with wheezing. The similarity of Wever's findings to our own supports the assumption that in Ansonia, too, air pollution may be the 'urban factor' responsible for increased symptoms in lifetime urban nonsmokers.

Expanding the pollution contrast

We have examined the effects of greater air pollution contrasts than existed between Ansonia and Lehanon in three ways: (1) by considering health effects of high indoor pollutant levels in homes, (2) by comparing our findings with those of others, in areas with pollutant concentrations higher than those in Ansonia, (3) by examining respiratory health data from people living in clean rural areas.

Fig. 1 Per cent prevalence of usual phlegm by sex, age, smoking and residence (LR, PU and LU explained in Table 2). Predicted prevalences are those obtained from the model summarised in Table 3. Only significant variables are shown, for example, smokers were not subdivided according to residence as this variable was only significant among nonsmokers.



(1) Suspended particulates indoors are predominantly small-sized ($<1 \mu\text{m}$ diameter) and thus able to penetrate into small bronchi and alveoli¹⁹. Hence, with equal TSP concentrations, indoor air might be more damaging to health than outdoor air, in which large particles are kept suspended by air currents. However, we found no evidence that the high TSP levels (up to $400 \mu\text{g m}^{-3}$) in homes with smokers (ref. 20 and H. R. Hosein *et al.*, unpublished observations) were associated with increased symptoms or lung function loss among nonsmokers in the same

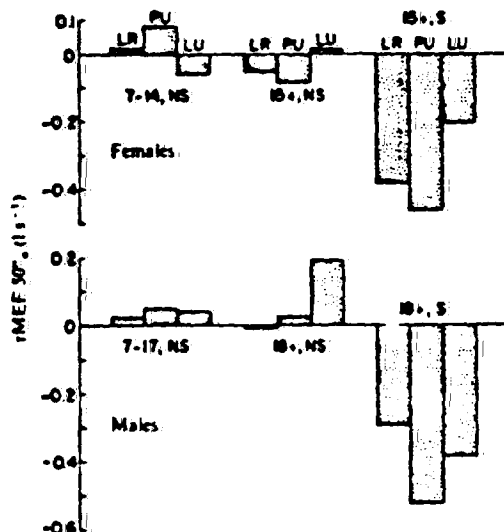


Fig. 2 Mean residual MEF50% (instantaneous maximum flow at 50% FVC). Residual (rMEF50%) = observed - predicted value. None of the differences between residential groups (LR, PU, LU, see Table 2) are significant in any of the six groups by sex, age and smoking habits. For boys and girls, this was also true when a further subdivision was made according to age (7-9 yr, 10-14 yr, 15-17 yr), and differences between LR, PU and LU residents were examined within each of these age and sex groupings. Differences between adult smokers and nonsmokers were significant within each residential subgroup (for example, LR smoking compared with nonsmoking males or females). For purposes of illustration, MEF50% is shown in l.s^{-1} . The statistical analyses were, however, done on residuals in transformed units. In MEF50% in children and $\sqrt{\text{MEF50\%}}$ in adults, these transformations were required to obtain satisfactory prediction equations (see ref. 12 for the equations and their derivation). The equations with transformed units provide residuals which are normally distributed and have equal variances independent of age, height and weight within each subgroup by sex and age group. Values for s.e.m. residuals range over 0.037-0.085 in females and boys, and 0.1113-0.1755 in adult male groups. Differences between mean residuals in smoking groups may reflect differences in amounts smoked, although differences in amounts smoked were not significant between residential groups. PU men and women smoked more than LR and LU men and women.

homes. Nor did we find evidence for loss of lung function among children living in homes with parents who smoked²¹. Thus, much higher TSP concentrations than those which occurred outdoors in Ansonia may still be subthreshold with respect to health effects.

(2) SO_2 and TSP concentrations have previously been high in many urban areas. In the UK, very high pollution levels (up to $1,160 \mu\text{g m}^{-3} \text{SO}_2$) which occurred in 1965 and previous years, were clearly associated with exacerbations of bronchitis²². However, pollution levels lower than those in the UK in the 1950s and early 1960s do not seem to have any marked effect on health. For example, results similar to ours (a slight excess of cough and phlegm) were obtained among men employed in Manhattan in 1962-63 (ref. 23), before current air pollution control programmes began, and at a time when SO_2 and TSP

were of the order of $500 \mu\text{g m}^{-3}$ and $250 \mu\text{g m}^{-3}$, respectively¹³. At about the same time (1961-62), nonsmoking black and white male postal or transit workers in New York City^{24,25} had $\text{FEV}_{0.6}$ values almost identical to those in our urban and rural nonsmokers in 1973 when age, race and height are taken into account. According to our equations describing growth of lung function in children¹², Czech children (age 10-11 yr) living in a town with high SO_2 (annual mean $150-170 \mu\text{g m}^{-3}$)²⁶ and TSP (annual mean $100-110 \mu\text{g m}^{-3}$)²⁶ concentrations have lung function values²⁷ very close to those of 10-11-yr-old children in Ansonia and Lebanon.

Oxidant pollution has not been clearly linked with increased prevalence of chronic bronchitis or its component symptoms; in fact, chronic bronchitis seems to be about as uncommon among Los Angeles nonsmokers²⁸ as among our rural (LR + PU) nonsmokers of the same age (45-64 yr), that is, 1.7 and 1.5%, respectively. Nonsmokers in Los Angeles, exposed to higher oxidant and TSP concentrations, and nonsmokers in Connecticut have similar lung function when height is taken into account (Table 4).

(3) The lack of important contrasts in air pollution and respiratory health between Ansonia and Lebanon might be explained if Lebanon were a relatively polluted rural area. However, we have found no evidence that respiratory health is demonstrably better in pristine rural areas. Nonsmokers in such an area (Chilliwack, British Columbia) had higher prevalences of cough and phlegm²⁹ than our lifetime urban nonsmokers. Residents of Winnsboro, South Carolina (with significantly lower SO_2 and NO_2 concentrations than those of Lebanon³) had symptom prevalences and lung function similar to those of Lebanon residents, and a higher prevalence of a history of asthma (unpublished observations). Black children and adults in a primitive village in Upper Volta, away from cities and with minimal automotive traffic³⁰, had FVC and $\text{FEV}_{0.6}$ values similar to those we recorded among urban black residents in Ansonia and rural black residents in South Carolina.

We conclude from these comparisons between our data and those of others that even relatively low levels of air pollution (as in Ansonia) may be associated with a slight excess of some respiratory symptoms in nonsmokers, but that these symptoms may only become noticeably worse when SO_2 and particulates reach levels higher than those prevailing in Manhattan in 1962-63. Even high concentrations of SO_2 , TSP and oxidants by current US standards are not associated with loss of lung function when sex, race, age, height and weight are adequately taken into account.

Implications

The overall impact of outdoor air pollution on respiratory health in Ansonia residents seems to be minimal. Even though the levels of air pollution in Ansonia are low by the standards of the UK in the 1950s, this is of interest because Connecticut is frequently said to have "the worst air pollution in the country outside Los Angeles" (ref. 31). However, any effect of air pollution in Ansonia is small compared with the effects of cigarette smoking and of certain occupational exposure hazards, such as occur among cotton textile workers³². Nor have we found evidence that outdoor air pollution worse than that in Ansonia (for example, in Los Angeles³³, New York^{33,34,35}, Rotterdam³⁶ or Czechoslovakia^{37,38}) produces substantially greater effects on health. Our conclusions are valid for those lung disorders which affect vital capacity and air flow rates; these include asthma, bronchitis and emphysema. There may be sensitive subgroups within the general population which we have not been able to detect, but this remains speculation.

The extent to which communities want to abate air pollution, and the economical burdens which they are willing to accept for that purpose, are matters for society to decide. There are many reasons, aesthetic as well as hygiene-related, for reducing urban air pollution. Within rather wide margins, however, variations in air quality do not seem to have substantial effects on the

prevalence and severity of common diseases which affect airway calibre.

We thank C. A. Mitchell and R. S. F. Schilling for help with the field studies; M. Callaway, D. Freeman, S. Gershman, L. Hayes and M. M. McGill for technical assistance; H. R. Hosein, P. J. Lawther and C. White for comments on the manuscript; and the National Heart, Lung and Blood Institute, USPHS, for financial support (HL-14179; HR-42912 and HL-21352).

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Molecular structure of a double helical DNA fragment intercalator complex between deoxy CpG and a terpyridine platinum compound

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The crystal structure of a complex containing deoxy CpG and a terpyridine platinum compound (TPH) shows a DNA double helical fragment with TPH intercalated between two Watson-Crick GC base pairs. The DNA unwinding angle is 23° and the pucker of the deoxyribose rings differ at the 3' and 5' ends.

STUDY of the molecular structure of nucleic acid components is of considerable interest in developing an understanding of the macromolecular nucleic acids. Single crystal X-ray diffraction analysis allows us to determine unambiguously several geometrical details concerning these molecules. Studies from this laboratory¹⁻⁴ showed that it was possible to crystallise self-complementary ribonucleoside phosphates as double helical fragments with Watson-Crick hydrogen bonding between the bases. An interesting application of these studies is their extension to double helical fragments which crystallise with planar molecules intercalated between their base pairs. Lerman⁵ postulated that certain classes of planar molecules, many of which are mutagenic or carcinogenic, act by insertion between adjacent base pairs in the DNA double helix. Several structural studies have supported this interpretation. Sobell and his colleagues^{6,7} described the structure of an RNA double helical fragment which contained an intercalator and several different structures of this type have now been solved with a variety of

intercalators lodged inside double helical ribonucleotide fragments⁸⁻¹¹. These crystallographic studies show that the pucker of the ribose ring is modified by the insertion of an intercalator between the base pairs. However, a major difference between DNA and RNA double helices is the different pucker of the sugar ring. It is therefore of interest to ask how intercalation will modify the geometry of the DNA backbone especially with regard to the pucker of the deoxyribose ring¹².

In this article we report the crystal structure of a complex containing deoxycytidylyl-(3',5')-deoxyguanosine (deoxy CpG) which has crystallised with the intercalator 2-hydroxyethanethiolato-2,2',2"-terpyridine-platinum (II) [TPH]^{13,14}. In this structure, deoxy CpG forms an antiparallel double helix in which the helix has unwound and the base pairs are unstacked with one TPH molecule intercalated between the base pairs of the double helical fragment. Another TPH molecule is stacked between double helical fragments in the lattice. This structure allows us to determine directly both the unwinding angle of the DNA double helical fragment as well as the pucker of the deoxyribose rings.

Experimental methods

The dimer deoxy CpG was prepared using the phosphotriester method^{15,16}. The dimer thus obtained was converted into the ammonium salt by passing it twice over a Dowex cation-exchange resin in the NH₄⁺ form. The material was freeze dried

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Shephard, R.J., Collins, R., Silverman, F. "Responses of Exercising Subjects to Acute "Passive" Cigarette Smoke Exposure" Environmental Research 19: 279-291, 1979.

SUMMARY: Responses to 2 hr of "passive" cigarette smoke exposure have been tested in 23 healthy young men and women who were performing intermittent bicycle ergometer work sufficient to increase respiratory minute volumes by a factor of 2.5. A simple crossover design compared data with reactions to sham exposures of similar duration. Cigarettes were smoked by a standard machine, chamber carbon monoxide concentrations were 20 (moderate dose) or 31 ppm (heavy exposure). Symptoms were much as in moderate exposures without exercise. The main complaints were of odor and eye irritation. Cough, nasal discharge or stuffiness, and throat irritation were also reported, but wheezing, shortness of breath, and tightness in the chest were both uncommon and unsupported by objective evidence of bronchospasm. A small increase of tidal volume and respiratory minute volume seemed due to anxiety rather than airway irritation. Static lung volumes were unchanged, but there were small (3-4%) decreases of FVC, FEV1.0, Vmax 50%, and Vmax25%. The changes of dynamic lung volumes were of the order anticipated from the "cigarette equivalent" encountered by the passive smoker (< 1/2 cigarette in 2 hr.).

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Responses of Exercising Subjects to Acute "Passive" Cigarette Smoke Exposure

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Responses to 2 hr of "passive" cigarette smoke exposure have been tested in 23 healthy young men and women who were performing intermittent bicycle ergometer work sufficient to increase respiratory minute volumes by a factor of 2.5. A simple crossover design compared data with reactions to sham exposures of similar duration. Cigarettes were smoked by a standard machine; chamber carbon monoxide concentrations were 20 (moderate dose) or 31 ppm (heavy exposure). Symptoms were much as in moderate exposures without exercise. The main complaints were of odor and eye irritation. Cough, nasal discharge or stuffiness, and throat irritation were also reported, but wheezing, shortness of breath, and tightness in the chest were both uncommon and unsupported by objective evidence of bronchospasm. A small increase of tidal volume and respiratory minute volume seemed due to anxiety rather than airway irritation. Static lung volumes were unchanged, but there were small (3-4%) decreases of FVC, FEV₁, \dot{V}_{max} , and \dot{V}_{max} . The changes of dynamic lung volumes were of the order anticipated from the "cigarette equivalent" encountered by the passive smoker (<1 cigarette in 2 hr).

INTRODUCTION

Appreciable atmospheric concentrations of particulate matter, irritant gases, and vapors can develop due to the accumulation of tobacco smoke in poorly ventilated buildings (for references, see Sebben *et al.*, 1977; Pimm *et al.*, 1978; Shephard *et al.*, 1978a). The "passive" exposures to cigarette smoke are subjectively unpleasant for most nonsmokers plus some continuing and former smokers (Johansson and Rouge, 1965; Anderson and Dalhamn, 1973; Weber-Tschopp *et al.*, 1976; Shephard and LaBarre, 1978), leading to irritation of the eyes and nose (Shephard *et al.*, 1978b,c) and instability of the tear film (Basu *et al.*, 1978). Some authors have also described cardiac and respiratory symptoms (Aronow, 1978; Surgeon General, 1972; Pimm *et al.*, 1977, 1978), an increased incidence of respiratory infections in the children of smoking parents (Norman-Taylor and Dickinson, 1972; Cameron and Robertson, 1973; Colley, 1974; Harlap and Davies, 1974), and an increased risk of lung cancer (British Medical Journal, 1978). However, other investigators have stressed that the increase of ambient CO concentration in a room contaminated by cigarette smoke is quite small (Fischer *et al.*, 1978), particularly if allowance is made for the effect of interfering vapors such as ethanol (First and Hinds, 1976) upon the usual CO-measuring instrument (the "Ecolyser"). Further, one recent study has failed to confirm the supposed effect of parental smoking upon the respiratory health of children (Schilling *et al.*, 1977).

Experimental exposures to moderate concentrations of cigarette smoke have demonstrated only small changes of pulmonary function, in some instances statistically significant, but of doubtful biological importance (Pimm *et al.*, 1978). Since

changes of respiratory mechanics are an early acute response to smoking in both smokers and nonsmokers (Nadel and Comroe, 1961; Clarke *et al.*, 1970; Da Silva and Hamosh, 1973; Hamosh and Da Silva, 1977), it was decided to examine the pulmonary reactions of the "passive" smoker under more adverse conditions than those previously evaluated. The respiratory minute volume during exposure was increased by intermittent moderate exercise, and in a final series of experiments the number of cigarettes burnt in the experimental chamber was also increased.

METHODS

Subjects and experimental plan. The subjects were 23 healthy young adult volunteers, drawn from the University of Toronto Community. Physical characteristics are summarized in Table 1. All were life-long nonsmokers (cigarette consumption nil for the past year, no history of smoking > one cigarette per day). None had any history of allergic disease.

A preliminary visit to the laboratory permitted clinical examination and familiarization of the subjects with the required test procedures. At comparable times on 2 subsequent days, subjects spent 2 hr in an exposure chamber, alternating 15-min periods of exercise sufficient to increase respiratory minute volume by a factor of 2.5 with sitting at rest. The chamber was filled with either ambient air (sham exposure) or cigarette smoke (experimental exposure), concentration being as in previous experiments (Pimm *et al.*, 1978) for the first 13 subjects and augmented by some 50% for the second group of 10 volunteers.

The protocol followed for the 2 exposure days is summarized in Table 2.

Exposure conditions. Details of the exposure chamber are given in a previous report (Pimm *et al.*, 1978). In brief, a standard cigarette smoking machine (Wander and Hofmann, 1967) was operated in a sparsely furnished 14.6 m³ chamber. A popular brand of 85-mm filter-type cigarette (tar and nicotine content 19 and 1 mg, respectively) was smoked by brisk (2-sec) controlled 35-ml draws to a length of 23 mm. For the first 13 subjects, four cigarettes were burnt initially followed by a further cigarette at half-hour intervals. For the second 10 subjects the initial combustion was increased to six cigarettes, again followed by the burning of one further cigarette at half-hour intervals.

The first pattern of combustion yielded a carbon monoxide concentration 20.0 ± 1.6 ppm for the men and 20.1 ± 2.4 ppm for the women, with particulate levels declining slowly from 4 to 2 mg/m³. With the six cigarettes, air contain-

TABLE 1
PHYSICAL CHARACTERISTICS OF SUBJECTS (MEAN \pm SD OF DATA)

	Age (years)	Height (cm)	Weight (kg)
Males			
(4 = 3 cigarettes, n = 6)	22.7 \pm 3.2	177.0 \pm 9.9	67.9 \pm 12.1
(6 = 3 cigarettes, n = 5)	23.4 \pm 4.0	172.4 \pm 9.0	73.6 \pm 22.1
Females			
(4 = 3 cigarettes, n = 7)	24.1 \pm 4.0	160.0 \pm 10.6	51.1 \pm 8.4
(6 = 3 cigarettes, n = 5)	27.4 \pm 5.1	160.0 \pm 12.4	50.2 \pm 8.4

Procedures

Changes in

Post-exposure

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TABLE 2
PROTOCOL FOR 2-Hr CHAMBER EXPOSURE TO AIR OR CIGARETTE SMOKE

Prechamber tests	Lung volumes by helium dilution (tidal VC, RV, FRC, ERV, TLC) Carboxyhemoglobin by rebreathing technique Resting ventilation (\dot{V}_E , f_R , V_T) Flow-volume curves (FVC, FEV _{1.0} , $\dot{V}_{max, 25\%}$, $\dot{V}_{max, 50\%}$) Resting electrocardiogram
Chamber tests	Pedal bicycle ergometer at load to increase \dot{V}_E to 2.5 times resting level 11–26 min, 41–56 min, 71–86 min, 101–116 min Flow-volume curves at 0, 5, 10, 30, 60, 90, 120 min Resting ventilation at 30, 60, 90, 100, 120 min Exercise ventilation at 54, 84, 114 min Electrocardiogram every 10 min, 20–120 min
Postexposure tests	Lung volumes by helium dilution Carboxyhemoglobin Symptom questionnaire

tion was some 50% greater, CO levels averaging 31.1 ± 4.3 ppm for the men, and 31.4 ± 4.0 ppm for the women.

Lung volumes. Functional residual capacity (FRC), expiratory reserve (ERV), residual volume (RV), and total lung capacity (TLC) were measured by means of the 7-min helium rebreathing technique (Collins respirometer/catharometer system).

Respiratory minute volume (\dot{V}_E), breathing frequency (f_R), and maximum expiratory flow-volume curves were obtained using a heated Fleisch (No. 3) pneumotachograph and integrator, volume and flow signals being displayed on a Tectronix storage oscilloscope. At each test period, the subject was seated, and performed three forced vital capacity (FVC) maneuvers, the curve with the largest FVC being used for analysis. In addition to FVC, measurements were taken of 1-sec forced expiratory volume (FEV_{1.0}) and the maximum flow at 25% ($\dot{V}_{max, 25\%}$) and 50% ($\dot{V}_{max, 50\%}$) of the vital capacity.

Exercise. Subjects performed standard intermittent exercise on a Von Döbeln bicycle ergometer. In order to avoid any complication from exercise-induced bronchospasm, the 15-min periods of exercise were displaced as far as possible from respiratory function measurements. Work loads were set to yield approximately a 2.5-fold increase of respiratory minute volume. Taking account also of the intervening 15-min rest periods, the average respiratory minute volume over the experiment was approximately 1.75 times the normal resting level. Heart rates during exposure were recorded by electrocardiogram (CM₅ lead, Shephard, 1977).

Symptoms. At the end of each exposure, subjects were asked to respond in a yes/no fashion to the presence of several potential symptoms (Table 3). In the event that a symptom was reported, they were then asked to rate its severity (trace, minimal, moderate, severe, or very severe).

Statistical analysis. All data were expressed as percentages of the preexposure reading for the corresponding day. Differences between test and control days were assessed using standard *t* tests.

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TABLE 3
 Static Lung Volumes to Cigarette Exposure—2-hr Experiments to 4, 3, and 6-3 Cigarettes with Determinations Performed

Symptom	4 + 3 Cigarettes (n = 12) ^a					6 + 3 Cigarettes (n = 10) ^b						
	Nil	Trace	Minimal	Moderate	Severe	Very severe	Nil	Trace	Minimal	Moderate	Severe	Very severe
Use of medication	12	0	0	0	0	0	10	0	0	0	0	0
Chlor	0	0	1	5	2	2	1	0	0	1	1	0
Nausea	12	0	0	0	0	0	10	1	1	0	0	0
Cough	5	2	4	1	0	0	6	1	1	2	0	0
Sputum	11	1	0	0	0	0	0	0	0	0	0	0
Soreness												
Substernal	12	0	0	0	0	0	9	0	1	0	0	0
Muscular	12	0	0	0	0	0	10	0	0	0	0	0
Other	12	0	0	0	0	0	10	0	0	0	0	0
In total	7	0	2	0	0	0	7	1 ^a	1	1	0	0
Shortness of breath	10	1	0	1	0	0	8	1	0	1	0	0
Nasal discharge or stiffness	0	2	1	1	0	0	4	1	1	2	1	0
Wheezing	12	0	0	0	0	0	9	1	0	0	0	0
Tightness in chest	12	0	0	0	0	0	9	0	1	0	0	0
Hoarseness	9	1	2	0	0	0	6	2	1	1	0	0
Fatigue	10	1	0	1	0	0	8	0 ^a	2 ^a	0	0	0
Eye irritation	1	1	1	1	6	2	1	0	1	0	4	0
Headache	9	0	2	1	0	0	7	0	1	1	1	0
Other	12	0	0	0	0	0	0	0	0	0	0	0
Total	165	12	13	11	0	3	115	11	11	9	9	0

Symptoms

At both 4 (Table 3) and 6 (Table 3) wheezing at flow volume resting and control values.

Awarding subjects (11 total of 123) subjects exp of 134 points.

Cardiorespiratory

The respiratory entered the increased by cigarette exposure during exercise 0.025). In each average experimental statistics. In during exercise.

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Static Lung Volumes

In both the static lung volumes a slight suggestion of volume and trend was static.

Dynamic Lung Volumes

The pre-exposure and experimental during exposure.

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RESULTS

Symptoms

At both levels of exposure, the main complaints were of odor and eye irritation (Table 3). Even at the highest dose, only one subject (D.K.) complained of wheezing and tightness in the chest; he did not show any unusual impairment of flow-volume curves, although at the end of the 2-hr exposure (120, 114 min) his resting and exercise \dot{V}_E were 143% and 154%, respectively, of the corresponding control values.

Awarding points of 0 to 5 according to the severity of the symptoms reported, 12 subjects (1 subject failed to report the symptoms encountered), accumulated a total of 123 points (10.3 points/subject) at the lower level of exposure, while the 10 subjects exposed to the higher smoke concentration had a marginally greater score of 138 points (13.8 points/subject).

Cardiorespiratory Performance

The respiratory minute volume of most subjects was quite high before they entered the exposure chamber (Table 4). Nevertheless, values were further increased by the cigarette smoke but not by the sham exposure. In the 4 + 3 cigarette experiments, the increase of ventilation relative to sham averaged 9.6% during exercise (NS), and was 21.4% during the intervening rest periods ($P > 0.025$). In calculating the significance of these trends, data for each individual have been averaged over time, and the difference between these averaged responses for experimental and sham exposures has been calculated by standard two-tailed t statistics. In the 6 - 3 cigarette experiments, the effect was no greater (11.1% during exercise, NS; 12.5% during recovery, NS).

Any increase of respiratory minute volume was almost entirely attributable to an increase of tidal volume. The initial, preexposure respiratory rate was greater than normal. Comparing sham and experimental exposures, cigarette smoke was associated with an insignificant decrease of f_R during exercise (-1.8 and -6.4% at the two exposure levels), while during the recovery intervals there was an insignificant increase (3.4 and 3.7% at the two levels).

The heart rate was higher before the experimental than before the sham exposures (Table 5; for women in 4 + 3 cigarette experiment, $P < 0.01$, for men in 6 + 3 cigarette experiment $P < 0.025$). However, while actually exposed to the cigarette smoke both the increment of heart rate and the absolute heart rate were less than in the corresponding sham exposure.

Static Lung Volumes

In both the 4 + 3 and the 6 + 3 cigarette experiments (Table 6), the preexposure static lung volumes did not differ between sham and experimental days. There was a slight suggestion that cigarette smoke led to a decrease of expiratory reserve volume and functional residual capacity as indicated by helium mixing, but this trend was statistically insignificant.

Dynamic Lung Volumes

The preexposure dynamic lung volumes (Table 7) did not differ between sham and experimental days. In the 4 - 3 cigarette experiments, all results obtained during exposure were somewhat depressed on experimental days relative to sham

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TABLE 4
 RESPIRATORY MINUTE VOLUME (\dot{V}_E) AND BREATHING FREQUENCY (f_R)

Variable		Precapnure period	Exposure period	
			Rest ^a (%)	Exercise ^b (%)
4 + 3 Cigarette experiment (n = 11) ^c				
\dot{V}_E	(S)	Men: 16.1 ± 4.7 l · min ⁻¹ Women: 8.7 ± 2.0 l · min ⁻¹	105.7	241.7
	(E)	Men: 96 ± 29% Women: 105 ± 21%	128.3 ^d	264.0
f_R	(S)	Men: 25 ± 8 breaths · min ⁻¹ Women: 17 ± 4 breaths · min ⁻¹	103.3	128.3
	(E)	Men: 102 ± 33% Women: 94 ± 30%	106.8	126.0
6 + 3 Cigarette experiment (n = 7) ^c				
\dot{V}_E	(S)	Men: 14.8 ± 4.6 l · min ⁻¹ Women: 11.3 ± 2.9 l · min ⁻¹	95.4	214.3
	(E)	Men: 92 ± 32% Women: 77 ± 26%	107.3	236.3
f_R	(S)	Men: 14.7 ± 3.1 breaths · min ⁻¹ Women: 20.5 ± 5.3 breaths · min ⁻¹	96.2	162.3
	(E)	Men: 92 ± 30% Women: 124 ± 52%	99.8	152.0

^a Mean ± SD of data for (a) preexposure period in sham exposure S (absolute values, l · min⁻¹ BTPS and breaths · min⁻¹), (b) preexposure in experimental exposure E (percentage of sham preexposure period), and (c) sham and experimental exposures (percentage of corresponding preexposure period).

^b Resting data for 30, 40, 60, 90, 100, 120 min of exposure averaged. Exercise data for 34, 64, 114 min of exposure averaged. Individual data with SD available on request.

^c Complete data not available for remaining subjects.

^d Increase over sham exposure: $P < 0.025$.

days, with a 5.6% decrease of FVC ($0.2 > P > 0.1$), a 3.3% decrease of FEV₁ (< 0.05), a 4.2% decrease of $\dot{V}_{max, 50\%}$ ($0.1 > P > 0.05$), and a 4.8% decrease of $\dot{V}_{max, 25\%}$ ($0.2 > P > 0.1$). There was little evidence of adaptation to the cigarette smoke over the 2-hr exposure—indeed, the final results showed a slightly greater fractional loss than those observed in the first few minutes of the experiment.

In the 6 + 3 cigarette experiments, the FVC again tended to be depressed (average change 3.2%, NS), as was the $\dot{V}_{max, 50\%}$ (average change 8.0%). Changes in the $\dot{V}_{max, 25\%}$ and FEV_{1,0} were variable and statistically insignificant.

DISCUSSION

Severity of Dosage

The levels of passive cigarette smoke exposure selected for this investigation were not the highest reported values for contaminated rooms and vehicles; authors have encountered CO concentrations of 60–156 ppm (Wahl, 1967; Harmsen and Effenberger, 1957; Srch, 1967; Hoegg, 1972; Harke, 1972).

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TABLE 3
HEART RATE DATA*

Type of exposure		Preexposure period	Exposure period	
			Rest ^a (%)	Exercise ^a (%)
4 - 3 Cigarette experiment (n = 10) ^c				
(S)	Men	72 = 8 beats · min ⁻¹	121.3	177.0
	Women	77 = 15 beats · min ⁻¹		
(E)	Men	106 = 8%	100.9	137.8
	Women	115 = 7%		
6 - 3 Cigarette experiment (n = 9) ^c				
(S)	Men	64 = 8 beats · min ⁻¹	116.9	170.3
	Women	74 = 9 beats · min ⁻¹		
(E)	Men	124 = 18%	112.3	156.3
	Women	109 = 20%		

* Mean ± SD for (a) preexposure period in sham exposure S (absolute values, beats · min⁻¹), (b) preexposure period in experimental exposure E (percentage of sham preexposure period), and (c) sham and experimental exposures (percentage of corresponding preexposure period).

^b Resting data for 30, 40, 60, 70, 90, 100, 120 min of exposure averaged. Exercise data for 20, 50, 80, 110 min of exposure averaged. Individual data with SD available on request.

^c Complete data not available for remaining subjects.

^d Increase over sham exposure, $P < 0.01$.

^e Increase over sham exposure, $P < 0.05$.

Nevertheless, they seem realistic in the context of air quality criteria, representing the greatest likely hazard that would be encountered by a person undertaking moderate physical work in a smoke-contaminated and poorly ventilated room such as a tavern (Sebben *et al.*, 1977).

Symptoms Reported

Complaints arise in aircraft, trains, and buses when cigarette-induced increments of carbon monoxide concentration reach about a fifth of the values used in the present experiments (Sebben *et al.*, 1977; Shephard and LaBarre, 1978; Shephard *et al.*, 1978a). Furthermore, the complainants are usually sitting, rather than undertaking intermittent exercise. It is thus hardly surprising that our subjects had some complaints. What is more interesting is that as in more moderate exposures, comments often remained confined to odor and eye irritation. About a half of the subjects noticed some coughing, and there were also reports of nasal discharge or stuffiness and throat irritation. However, only one subject had responses indicative of bronchospasm (wheezing and shortness of breath). The rarity of a subjectively detectable increase of airway resistance may be explained on the basis that subjects undertaking light work fail to detect less than a fourfold increase of airway resistance (McKerrow *et al.*, 1958).

An increase in the initial combustion of cigarettes did not lead to any great increase in the number or severity of reported symptoms. Possibly, there was a saturation or adaptation of the receptors concerned. Certainly, conjunctival irritation was most marked on first entering the exposure chamber, and became less

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TABLE 6
STATISTICAL VARIATION^a

Measurement		Related vital capacity	Expiratory reserve volume	Functional residual capacity	Residual volume	Total lung capacity
4 x 3 Cigarette experiment (n = 7, 10) ^b						
(S)	Pre Exp men	3.26 ± 1.11	1.86 ± 0.65	1.73 ± 1.02	1.87 ± 0.72	7.13 ± 1.17
	women	3.47 ± 0.58	1.23 ± 0.15	2.17 ± 0.68	1.14 ± 0.51	4.74 ± 0.99
	Exp men + women	102.7 ± 6.9%	107.4 ± 11.6%	101.0 ± 14.3%	98.7 ± 27.9%	99.9 ± 10.1%
(E)	Pre Exp men	100 ± 1%	107 ± 8%	96 ± 17%	88 ± 12%	96 ± 11%
	women	101 ± 3%	106 ± 10%	94 ± 7%	96 ± 9%	97 ± 9%
	Exp men + women	101.2 ± 3.9%	95.6 ± 6.9%	96.7 ± 12.7%	102.2 ± 12.9%	99.9 ± 6.9%
6 x 3 Cigarette experiment (n = 7, 6) ^b						
(S)	Pre Exp men	3.74 ± 0.56	1.71 ± 0.41	2.88 ± 0.64	1.17 ± 0.24	6.90 ± 0.61
	women	3.17 ± 0.15	1.16 ± 0.06	2.29 ± 0.11	1.13 ± 0.16	4.43 ± 0.08
	Exp men + women	102.9 ± 4.8%	100.9 ± 13.6%	103.7 ± 14.3%	109.3 ± 20.0%	103.1 ± 3.1%
(E)	Pre Exp men	100 ± 1%	84 ± 17%	96 ± 4%	111 ± 20%	101 ± 3%
	women	106 ± 2%	118 ± 25%	106 ± 13%	96 ± 6%	101 ± 8%
	Exp men + women	101.2 ± 2.3%	95.7 ± 16.6%	98.2 ± 8.1%	100.5 ± 15.6%	101.0 ± 2.0%

^a Mean ± SD of data for (a) preexpiratory period in sham exposure (S) absolute values, (b) preexpiratory period in experimental exposure E (percentage of sham preexpiratory period), and (c) sham and experimental exposures (percentage of corresponding preexpiratory period).

^b Complete data not available for remaining subjects.

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as the experiment continued. The corneal pain receptors normally show a slow rate of adaptation, but it may be that the smoke became less irritant because it stimulated an increased lachrymal secretion (Shephard *et al.*, 1978c).

There is also a possibility that some or all of the other symptoms were "suggested" by the odor of cigarette smoke. In particular, it is surprising that the subject reporting wheezing and shortness of breath during exposure showed no significant decrement of objective measures of lung function. While this person may have had an unusual sensitivity to cigarette smoke, his symptoms could also have developed through a process of self-suggestion. There is thus scope for a definitive experiment relating objective measures of hypnotic susceptibility to the reported symptoms and physiological responses of the passive smoker.

Hyperventilation

At first inspection, the increase of respiratory minute volume during cigarette smoke exposure might seem to be objective evidence of airway irritation by the smoke particles. However, further examination of the data shows that this is an unlikely explanation, since the increment of \dot{V}_E was attributable entirely to an increase of \dot{V}_T . Stimulation of tracheal irritant receptors should curtail inspiratory drive, with a decrease of tidal volume and a compensatory increase of respiratory rate. We have described this pattern of response during inhalation of an irritant gas such as ozone (Folinsbee *et al.*, 1975). The increase of tidal volume could conceivably be attributed to a greater peripheral drive (for example, an action of absorbed nicotine upon the carotid chemoreceptors). However, the preexposure hyperventilation, the decreasing discrepancy between sham and experimental days as the exposure continued and the absence of a dose/response relationship all support an alternative hypothesis (a central facilitation of inspiratory drive by anxiety). A similar explanation would cover the slight tachycardia previously described in female subjects during exposure (Pimm *et al.*, 1978), and seen here before subjects entered the exposure chamber.

Static and Dynamic Lung Volumes

Static lung volumes show no consistent reaction to cigarette smoke exposure. However, the 4 + 3 cigarette experiments suggest a small decrement of dynamic lung volumes consistent with a small and practically unimportant decrease of airway conductance, while the 6 + 3 cigarette exposures induce statistically insignificant trends in the same direction.

Since dynamic airflow measurements depend upon the cooperation of the individual, it could be argued that there was some voluntary limitation of forced expiratory efforts in the smoke-filled room. Nevertheless, there are several pointers to a true pharmacological response:

(a) The male subjects in our previous resting exposures also showed a small decrease of \dot{V}_{max} and \dot{V}_{max} (Pimm *et al.*, 1978).

(b) The variance of the dynamic airflow measurements was comparable in experimental and sham exposures.

(c) The extent of flow impairment was consistent with previous observations made during active smoking.

Although Nadel and Comroe (1961) reported a 31% decrease of airway conductance in response to the smoking of a single cigarette, most authors have found

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TABLE 7
CHANGES IN DYNAMIC LUNG VOLUMES DURING SMOKING (S) AND EXPERIMENTAL (E) EXERCISES*

Prepressure			5 min (%)	120 min (%)	Average of seven observations ^a	
4 + 3 Cigarette experiment in ~ 12r						
FVC	(S)	Men	5.55 ± 1.69 liter	98.9 ± 6.4	99.7 ± 9.3	99.0
		Women	3.29 ± 0.57 liter			
	(E)	Men	97 ± 11%	94.1 ± 7.5	92.3 ± 4.1	93.5
		Women	106 ± 7%			
FEV _{1.0}	(S)	Men	4.17 ± 0.44 liter	101.7 ± 1.8	101.3 ± 7.0	101.7
		Women	2.94 ± 0.38 liter			
	(E)	Men	93 ± 14%	95.7 ± 12.2	101.1 ± 9.1	98.3 ^c
		Women	100 ± 8%			
$\dot{V}_{max\ 100}$	(S)	Men	3.65 ± 0.64 liter · sec ⁻¹	110.6 ± 19.7	110.2 ± 19.6	109.0
		Women	3.66 ± 0.92 liter · sec ⁻¹			
	(E)	Men	109 ± 30%	104.0 ± 9.4	102.7 ± 15.0	104.4 ^c
		Women	95 ± 15%			
$\dot{V}_{max\ 50}$	(S)	Men	1.79 ± 0.38 liter · sec ⁻¹	109.0 ± 22.9	113.1 ± 26.9	109.3
		Women	1.96 ± 0.27 liter · sec ⁻¹			
	(E)	Men	108 ± 36%	101.6 ± 10.7	106.4 ± 20.1	103.0
		Women	90 ± 12%			
6 + 3 Cigarette experiment in ~ 12r						
FVC	(S)	Men	4.08 ± 1.14 liter	101.9 ± 1.1	100.0 ± 1.0	101.0
		Women	2.70 ± 0.67 liter			
	(E)	Men	110 ± 25%	100.0 ± 8.1	101.1 ± 4.1	95.6
		Women	100 ± 3%			
FEV _{1.0}	(S)	Men	3.21 ± 0.96 liter	101.7 ± 1.1	101.1 ± 1.1	101.4
		Women	2.70 ± 0.67 liter			

	(F)	Men	108 ± 36%	104.6 ± 10.7	105.4 ± 20.1	104.0
		Women	90 ± 12%			
6 + 3 Cigarette experiment (n = 8)						
FVC	(S)	Men	5.08 ± 1.15 liter	101.9 ± 4.4	100.9 ± 4.9	101.0
		Women	2.70 ± 0.69 liter			
	(F)	Men	110 ± 22%	96.0 ± 8.3	99.4 ± 8.1	97.8
		Women	108 ± 4%			
FEV _{1.0}	(S)	Men	4.21 ± 0.96 liter	99.3 ± 9.4	101.1 ± 7.7	99.2
		Women	2.56 ± 0.56 liter			
	(F)	Men	95 ± 7%	99.4 ± 9.9	99.9 ± 7.0	100.6
		Women	98 ± 9%			
$\dot{V}_{max 25}$	(S)	Men	3.66 ± 1.21 liter · sec ⁻¹	102.6 ± 8.5	102.9 ± 10.9	100.5
		Women	4.13 ± 0.92 liter · sec ⁻¹			
	(F)	Men	109 ± 40%	105.3 ± 10.1	102.7 ± 15.9	103.9
		Women	95 ± 21%			
$\dot{V}_{max 75}$	(S)	Men	1.45 ± 0.57 liter · sec ⁻¹	104.9 ± 16.9	112.1 ± 19.6	108.6
		Women	2.25 ± 0.44 liter · sec ⁻¹			
	(F)	Men	124 ± 51%	102.9 ± 20.4	105.1 ± 27.1	99.9
		Women	86 ± 16%			

* All data mean ± SD of values expressed as percentage of corresponding preexposure results. Findings pooled for men and women at each dose.

† Average based on observations after 0, 5, 10, 30, 60, 90, and 120 min of observation. Detailed data, with SD, available on request.

‡ Complete data not available for remaining subjects.

§ Change relative to sham $P < 0.025$.

|| Change relative to sham $P < 0.05$.

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White, J.R., Froeb, H.F. "Small-airways Dysfunction in Nonsmokers Chronically Exposed to Tobacco Smoke" The New England Journal of Medicine 302: 720-723, 1980.

ABSTRACT. We evaluated the effect of long-term passive smoking (involuntary inhalation of tobacco smoke by nonsmokers) and long-term voluntary smoking on specific indexes of pulmonary function in 2100 middle-aged subjects. Regardless of sex, nonsmokers chronically exposed to tobacco smoke had a lower forced mid-expiratory flow rate (FEF 25 to 75 per cent) and forced end-expiratory flow rate (FEF 75 to 85 per cent) than nonsmokers not exposed ($P < 0.005$). In addition, values in passive smokers were not significantly different from those in light smokers and smokers who did not inhale ($P < 0.005$). When we looked at the extent to which smoke exposure is related to graded abnormality, we found that nonsmokers in smoke-free working environments have the highest scores on spirometric tests; passive smokers, smokers who do not inhale, and light smokers score similarly and significantly lower; and heavy smokers score the lowest ($P < 0.005$). We conclude that chronic exposure to tobacco smoke in the work environment is deleterious to the nonsmoker and significantly reduces small-airways function.

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SMALL-AIRWAYS DYSFUNCTION IN NONSMOKERS
CHRONICALLY EXPOSED TO TOBACCO SMOKE

JAMES R. WHITE, Ph.D., AND HERMAN F. FROEB, M.D.

Abstract: We evaluated the effect of long-term passive smoking (involuntary inhalation of tobacco smoke by nonsmokers) and long-term voluntary smoking on specific indexes of pulmonary function in 2100 middle-aged subjects. Regardless of sex, nonsmokers chronically exposed to tobacco smoke had a lower forced mid-expiratory flow rate (FEF 25 to 75 per cent) and forced end-expiratory flow rate (FEF 75 to 85 per cent) than nonsmokers not exposed ($P < 0.005$). In addition, values in passive smokers were not significantly different from those in light smokers and smokers who did not inhale

($P < 0.005$). When we looked at the extent to which smoke exposure is related to graded abnormality, we found that nonsmokers in smoke-free working environments have the highest scores on the spirometric tests; passive smokers, smokers who do not inhale, and light smokers score similarly and significantly lower; and heavy smokers score the lowest ($P < 0.005$). We conclude that chronic exposure to tobacco smoke in the work environment is deleterious to the nonsmoker and significantly reduces small-airways function. (N Engl J Med. 1980; 302: 720-3.)

It is generally believed that infrequent and short-term exposure to pollutants in tobacco, such as carbon monoxide, nicotine, benzo(a)pyrene, and oxides of nitrogen, will not permanently alter pulmonary function in healthy adult nonsmokers. We tested two hypotheses: that nonsmokers chronically exposed at work to the pollutants in tobacco will score lower on tests of small-airways function than nonsmokers not chronically exposed to tobacco smoke; and that exposure to tobacco smoke will cause a graded abnormality in small-airways function in relation to the extent of smoke exposure.

METHODS

Subjects

To examine these hypotheses we used the scores on tests of mean forced mid-expiratory flow (FEF 25 to 75 per cent) and mean forced end-expiratory flow (FEF 75 to 85 per cent); these tests have proved effective in detecting small-airways disease in its early stages.¹⁻³ Forced vital capacity and forced expiratory volume in one second (FEV₁) were also studied.

Data were collected on 5210 cigarette smokers and nonsmokers who had been physiologically evaluated during a "Physical Fitness Profile" course sponsored by the Department of Physical Education, University of California, San Diego, between 1969 and 1979. Most of the subjects resided in San Diego, an area low in air pollution. Occupation and locations of work and residence according to zip codes were analyzed. There were no statistically significant differences between the groups in types of occupation or in working or living locations. Eighty-three per cent of the working subjects held professional, managerial, or technical positions, and the remainder were blue-collar workers. Personal habits, environmental pollution, and smoking habits were assessed from an extensive, self-administered questionnaire completed on two separate occasions. The reliability coefficients for the test and retest are greater than $r = 0.96$. Each subject's age, height, and weight were recorded, and they were categorized according to sex, exposure to tobacco smoke, and smoking habits.

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Presented in part at the Annual Meeting of the American College of Sports Medicine, Honolulu, Hawaii, May 1979.

From the original 5210 candidates, 2208 were disqualified because they indicated on the questionnaire that they had a history of pulmonary or cardiac disease, persistent cough, recent asthma, respiratory illness, or bronchial disturbances; that they had had occupational exposure to dust or other toxic fumes; that they had lived in a smoggy or industrial area; or that they had been employed in areas associated with industrial pollution. The 3002 remaining candidates were assigned to one of six groups according to their exposure to tobacco smoke (Table 1). From each group 200 men and 200 women were then randomly selected and assigned to the comparison groups. However, only 50 male and female subjects were available for the noninhaling smoking group (3), and so the total number of subjects reported on is 2100.

A single technician administered successive forced-vital-capacity maneuvers until reproducible curves were obtained on each subject with use of the Dotti Pulmonary Performance Analyzer (PA70). The fast vital-capacity spirogram achieving the greatest volume was used to calculate the forced vital capacity (FVC), the forced expiratory flow for one second (FEV₁), the forced mid-expiratory flow (FEF 25 to 75 per cent), and the forced end-expiratory flow (FEF 75 to 85 per cent) (Table 1).

Comparisons were made between the scores achieved by six groups of subjects matched for age and sex. Group 1 comprised nonsmokers who had neither lived in a house where tobacco smoking was permitted nor been employed in an enclosed working area that permitted smoking or routinely contained tobacco smoke. Group 2 comprised passive smokers, that is, nonsmokers who lived in a house where tobacco smoking was not permitted but had been employed for 20 years or more in an enclosed working area that permitted smoking and routinely contained tobacco smoke. Group 3 contained pipe, cigar, or cigarette smokers who did not inhale; Group 4, light smokers who had inhaled one to 10 cigarettes per day for 20 years or more; Group 5, moderate smokers who had inhaled 11 to 39 cigarettes per day for 20 years or more; and Group 6, heavy smokers who had inhaled more than 40 cigarettes per day for 20 years or more. Presumably, the subjects in these last four groups all worked in environments where smoking was permitted, since they themselves smoked at work.

To test the hypothesis that there was no difference between the pulmonary scores in each group, we used a statistical package called "SPSSH Release 6.02," which gave us a one-way analysis of variance. When the analysis of variance revealed a significant difference, the hypothesis was rejected. We then used the Student-Newman-Keuls multiple-comparison test to determine subgroups.⁴

Carbon Monoxide Levels in Working Environment

On the questionnaire the subjects who did not smoke indicated whether smoking was permitted in their working area and whether the air generally contained tobacco smoke. To obtain a more objective measure of true concentrations of smoke in the working areas, we placed a portable carbon monoxide analyzer (Ecolyzer, Ener-

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Table 1. Vital Capacities and Expiratory Flow Rate (Mean \pm S.D.) in Male and Female Smokers and Nonsmokers.

GROUP	No. of Subjects	Sex	Age yr	Height cm	FVC liters	FEV ₁ % predicted	FEV ₁ liters	FEV ₁ % predicted	FEF 25-75% liter/sec	FEF 25-75% % predicted	FEF 75-85% liter/sec	FEF 75-85% % predicted
1—Nonsmokers, no smoky environment	200	F	47.77 \pm 7.0	162.05 \pm 6.58	3.35 \pm 0.63	102	2.63 \pm 0.63	104	3.17 \pm 0.74	106	1.03 \pm 0.38	112
	200	M	48.8 \pm 7.59	176.3 \pm 7.77	4.91 \pm 0.75	102	3.72 \pm 0.65	103	3.78 \pm 0.79	104	1.22 \pm 0.35	120
2—Nonsmokers, smoky environment >20 yr	200	F	45.91 \pm 6.94	161.8 \pm 6.68	3.23 \pm 0.46	98	2.47 \pm 0.63	99	2.72 \pm 0.71*	93	0.78 \pm 0.36*	85
	200	M	49.1 \pm 7.61	176.02 \pm 6.55	4.78 \pm 0.77	99	3.54 \pm 0.61	98	3.30 \pm 0.77*	91	0.97 \pm 0.34*	95
3—Smokers not inhaling cigarettes, pipe, or cigars >20 yr	50	F	46.93 \pm 7.10	159.7 \pm 7.09	3.19 \pm 0.52	97	2.49 \pm 0.74	99	2.71 \pm 0.87*	92	0.78 \pm 0.43*	85
	50	M	47.6 \pm 7.38	174.5 \pm 7.42	4.63 \pm 0.86	96	3.34 \pm 0.76	99	3.32 \pm 0.86*	92	0.89 \pm 0.47	87
4—Smokers inhaling 1-10 cigarettes per day >20 yr	200	F	47.36 \pm 7.0	159.77 \pm 7.44	3.15 \pm 0.39	96	2.40 \pm 0.62	98	2.63 \pm 0.73*	89	0.76 \pm 0.31*	83
	200	M	48.5 \pm 7.51	175.9 \pm 7.44	4.58 \pm 0.77*	95	3.49 \pm 0.62*	97	3.23 \pm 0.78*	89	0.79 \pm 0.36*	77
5—Smokers inhaling 11-39 cigarettes per day >20 yr	200	F	45.72 \pm 6.87	160.6 \pm 6.99	2.80 \pm 0.38*	85	2.13 \pm 0.62*	85	2.29 \pm 0.70*	78	0.63 \pm 0.31*	69
	200	M	48.3 \pm 7.49	176.02 \pm 7.67	4.04 \pm 0.74*	84	3.08 \pm 0.61*	86	2.73 \pm 0.81*	76	0.69 \pm 0.29	68
6—Smokers inhaling >40 cigarettes per day >20 yr	200	F	45.98 \pm 6.73	159.26 \pm 7.29	2.55 \pm 0.38*	78	2.01 \pm 0.64*	80	2.12 \pm 0.72*	72	0.57 \pm 0.33*	62
	200	M	47.8 \pm 7.44	176.53 \pm 7.9	3.92 \pm 0.73*	82	2.77 \pm 0.60*	77	2.59 \pm 0.82*	72	0.61 \pm 0.31*	60
Prediction for age: 46.3 yr, height: 160.53 cm †	1050	F	46.61 \pm 6.94	160.3 \pm 6.99	3.28	—	2.52	—	2.94	—	0.92	—
Prediction for age: 48.3 yr, height: 175.77 cm †	1050	M	48.35 \pm 7.50	175.77 \pm 7.54	4.81	—	3.60	—	3.62	—	1.02	—

*Significantly different from values in nonsmokers ($P < 0.005$).†Predicted according to Morris.¹¹

getics Science, Elmsdorf, N.Y.) on top of the desk or in the working area of 40 randomly selected nonsmokers who had indicated that they worked in an environment without smoke and 40 similarly selected nonsmokers who had indicated that the air in their working area contained smoke from co-workers. Carbon monoxide, a component of tobacco smoke, is an accurate tobacco-smoke tracer,¹⁷ and its concentration is directly proportional to that of tobacco smoke.¹⁸ The mean carbon monoxide concentrations in areas where smoking occurred were compared with similar measurements taken in areas where smoking was not permitted (Table 2). During the day, particularly at 11:20 a.m. and 1:20 p.m., the differences in the mean values between environments with and without smoking were significantly different. Only at 7:00 a.m. and 7:00 p.m., before and after working hours, were carbon monoxide concentrations the same. In the environments where there was smoking, the mean concentration at peak values almost doubled, from 6.4 to 11.6 parts per million, whereas in the environments where there was no smoking, the increase was from 6.3 to 8.2 parts per million. The peak concentration of carbon monoxide was significantly greater in the environments where smoking occurred. The carbon monoxide analyzer was calibrated in the laboratory and found to have ± 2 per cent reproducibility and ± 2 per cent accuracy at levels between 0 and 50 parts per million.

Of the 80 working areas tested for carbon monoxide concentrations, 76 were air-conditioned. No attempt was made to determine the direction of the circulation of refrigerated air or the exact air exchange. Building codes require a minimum of five to six complete air exchanges per hour. The size of the rooms and the number of co-workers in the working areas were computed. In terms of these two factors, there was no significant difference between the working areas where smoking was permitted and where it was not permitted. In the areas without smoking, ventilation was sufficient to maintain peak carbon monoxide concentrations below 9 parts per million, which Holbrook¹⁹ defines as the upper limit for carbon monoxide in areas with adequate ventilation.¹⁹ However, ventilation in our study was not capable of adequately extracting polluted air as measured by carbon monoxide levels in areas where smoking was allowed (Table 2).

RESULTS

The mean values \pm the standard deviation for the FVC, FEV₁, FEF 25 to 75 per cent, and FEF 75 to 85 per cent in the six groups studied are shown in Table 1. There were no statistical differences in the ages and heights within the various groups.

Compared with nonsmokers who worked in environments where there was no smoking, both the men and the women in the other five groups had significantly lower values for FEF 25 to 75 per cent and FEF 75 to 85 per cent. These lower levels were observed in both absolute values and per cent predicted values calculated according to the formulas of Morris.¹¹ The FVC and FEV₁ were not as sensitive, and values were lower only in the female heavier smokers of Groups 5 and 6 and in the male heavier smokers of Groups 4, 5,

Table 2. Carbon Monoxide Concentrations (parts per million) Measured during the Workday.

TIME	SMOKING PERMITTED IN WORK AREA (40 SUBJECTS)		SMOKING NOT PERMITTED IN WORK AREA (40 SUBJECTS)		COMPARISON BETWEEN WORKING AREAS
	MEAN \pm S.D.	RANGE	MEAN \pm S.D.	RANGE	T VALUE
7:00 a.m.	6.4 \pm 2.9	3.1-10.9	6.3 \pm 1.7	3.3-10.3	0.1
10:00 a.m.	9.2 \pm 5.4	3.5-29.4	7.1 \pm 3.3	3.6-13.6	2.1*
11:50 a.m.	11.1 \pm 6.0	4.1-31.2	8.2 \pm 4.1	3.8-12.7	2.9†
1:20 p.m.	11.6 \pm 7.3	3.8-25.8	6.9 \pm 2.7	4.0-13.8	4.7†
4:20 p.m.	9.7 \pm 5.9	3.3-20.2	7.5 \pm 3.8	3.3-11.9	2.2*
7:00 p.m.	7.1 \pm 3.3	3.2-14.7	6.5 \pm 2.2	3.4-10.7	0.6

* $P = 0.05$ by unpaired t -test.† $P = 0.01$ by unpaired t -test.

and 6. The passive smokers not only scored significantly lower than their nonsmoking counterparts but also fell into the same state of impaired performance as the noninhalers and light smokers. Again, this was true for both men and women.

Table 1 shows the predicted values for the average man and woman according to height and weight. There is no statistical difference between these predicted values and the values in nonsmokers. However, as the degree of smoking exposure increased in both men and women, the performance of FEF 25 to 75 per cent and FEF 75 to 85 per cent decreased, as shown by the stepwise reduction in scores for moderate and heavy smokers (Table 1).

As shown in Table 3, differences in pulmonary performance between groups were analyzed by statistical analyses of variance according to the Student-Newman-Keuls multiple-range test at a level of

Table 3. Pulmonary Function in Subjects Chronically Exposed to Tobacco Smoke.*

VARIABLE	SEX	SUBGROUPS ARRANGED IN ORDER OF DECREASING PULMONARY FUNCTION
FVC	Female	NS NI LS PS MS HS
	Male	NS PS NI LS MS HS
FEV ₁	Female	NS NI LS PS MS HS
	Male	NS NI PS LS MS HS
FEF 25-75%	Female	NS PS NI LS MS HS
	Male	NS NI PS LS MS HS
FEF 75-85%	Female	NS PS NI LS MS HS
	Male	NS NI PS LS MS HS

*Underlinings indicate subgroups arranged by the Student-Newman-Keuls multiple-range test at the 0.005 level. For example, for FVC, female, there are three groups that differ from each other statistically: the first group comprises NS, NI, LS, and PS; the second group MS; and the third HS. NS denotes nonsmokers, PS passive smokers, NI noninhalers, LS light smokers (one to 10 cigarettes per day), MS moderate smokers (11 to 39 cigarettes per day), and HS heavy smokers (40 or more cigarettes per day) — Groups 1 to 6, respectively.

0.005.⁸ The subgrouping indicates that both male and female nonsmokers who live and work in a smoke-free environment score the highest of all the subgroups, and that passive smokers, smokers who do not inhale, and light smokers are not significantly different from one another. The analysis also shows that both moderate and heavy smokers are, in general, not significantly different: that is, they share about the same degree of dysfunction. It is impressive that in all pulmonary-function tests, the moderate and heavy smokers scored significantly worse than all other groups, and that in tests that best reflect small-airways function (FEF 25 to 75 per cent and FEF 75 to 85 per cent), the nonsmokers scored significantly better than all other groups.

DISCUSSION

We used several methods to minimize the standard error of the difference and eliminate sampling biases in this study. First of all, measurements were made in a large number of subjects (a total of 2100), and they were divided into six specific groups according to their responses to a questionnaire on smoking history. Candidates with health, environmental, or occupational conditions that could influence pulmonary function adversely were disqualified from the study. Furthermore, comparisons among the groups of occupations and working and living locations showed that they were not significantly different, thus minimizing the sampling error. When the sites for measurement of carbon monoxide were selected, bias was reduced because 20 male and 20 female nonsmokers and 20 male and 20 female passive smokers were randomly selected from the 200 subjects in each group. Finally, most studies on smoking have a correlational design; this approach may weaken many of the conclusions because tobacco smoking is a matter of choice and is done for a variety of personal reasons, which may cause both the smoking and the pulmonary dysfunction. In our study, neither the nonsmokers nor the passive smokers chose to smoke; therefore, the pulmonary dysfunction found in passive smokers cannot be attributed to the "reasons" that may be related to the dysfunction in smokers. Comparison between the nonsmokers and the passive smokers is thus truly experimental.

Although there was no statistical difference between the predicted values in Table 1 and values in the nonsmokers, it must be remembered that predicted values were based on the combination of data obtained from nonsmokers and passive smokers. When data on the nonsmoker and the passive smoker are arithmetically averaged, the value approximates that found in existing predicted norms. We believe that in choosing subjects for establishing "normal predicted values," one should take into account the degree of cigarette pollution in which the subjects live and work.

Ambient carbon monoxide may have deleterious effects on bodily functions other than those of the lung. Studies by Bridge and Corn⁹ and by Hexter and Goldsmith¹² have indicated that concentrations of carbon monoxide as low as 8 parts per million can increase the incidence of symptomatic or overt ischemic heart disease. It has also been shown that elevated carbon monoxide concentrations can increase the incidence of early angina in patients with atherosclerotic heart disease.^{13,14} High carbon monoxide concentrations also lead to alterations in psychomotor performance in healthy subjects.¹⁵ We chose to look at long-range changes in the function of small airways in the lungs of nonsmokers chronically exposed to low levels of tobacco smoke as measured by carbon monoxide levels. Carbon monoxide was used as an index of exposure to

tobacco smoke and was not intended to be identified as the specific inciting agent.

The traditional spirometric tests of FVC and FEV₁ depend mostly on the total airway resistance and elastic recoil of the lung and are often normal in the presence of extensive small-airways disease.¹⁴ In contrast, the mid-expiratory and maximal end-expiratory flow rates reflect expiratory flow in the presence of lower lung volumes during a period when airway segments may be in the process of closing.^{17,18} Other studies have indicated a high frequency of small-airways disease in relatively asymptomatic cigarette smokers.¹⁹ In one study, 72 per cent of the subjects had significantly decreased maximal mid-expiratory flow rates.¹ Morris^{2,20} has shown that measurements of forced expiratory flow rate are simple and accurate predictors of changes in small airways. It is generally agreed that in the presence of normal FVC and FEV₁, reduced forced mid-expiratory and end-expiratory flow rates are commensurate with small-airways disease.^{2,11,20} Our results agree with those of Macklem and Mead¹⁴ and of Morris,^{2,11,20} in that neither FVC nor FEV₁ was significantly different in passive smokers and nonsmokers, but that both FEF 25 to 75 per cent and FEF 75 to 85 per cent were significantly lower in passive smokers than in nonsmokers.

In considering the relation of graded abnormality to the extent of smoke exposure, it is interesting to note that the nonsmokers in our study scored well above all other groups in the tests in Tables 1 and 3. However, there was no significant difference in the scores of the passive smokers, the smokers who did not inhale, and the light smokers. This finding suggests that if long-term small-airways dysfunction is occurring, the nonsmokers who work in a smoky environment have about the same risk of impairment as do smokers who do not inhale and smokers who inhale between one and 10 cigarettes per day. Niewoehner et al.²¹ showed that further increases in exposure to cigarette smoke cause a progression from small-airways involvement to extensive bronchial and alveolar disease: the greater the exposure, the greater the involvement.

There is supporting evidence of the effects of passive smoking on small-airways function and the development of a graded abnormality according to extent of exposure to smoke. A recent study by Tager et al.²² has shown that children living in households where parents smoked tobacco had lower mid-expiratory flow rates (FEF 25 to 75 per cent) than children who lived in households where smoking did not occur. In addition, FEF 25 to 75 per cent in children who had never smoked declined as a function of the number of parents who smoked in the household.

The greater the exposure, the lower the pulmonary-function score.

Although many nonsmokers believe that exposure to tobacco smoke is irritating and generally obnoxious, our studies and Tager's show the adverse effects of passive smoking on the small-airways function of both adults and children. With these data now available, health officials and the medical profession must consider potential for small-airways dysfunction in nonsmokers chronically exposed to tobacco smoke.

We are indebted to Stanton A. Glantz, Ph.D., and Howard F. Hunt, Ph.D., for statistical collaboration, and to Mrs. Joan Cochrane for manuscript preparation and editing.

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this place from the inside, in the way that those of us who serve here do.

The press and media people pack the gallery upstairs during a debate on a pay raise, but they rarely write or speak about the personal ramifications of the job here. This is not to complain. Every Member here feels that it is a supreme honor to serve as a Member.

But it is important that the public know more about what kinds of people serve here, how hard they work, the personal toll that is taken on individuals and families.

I have seen grown men here cry when their marriages were destroyed. I have seen grown men depressed about missing events that were important to their children.

In sports they have a term called "playing hurt," when players participate even when injured. Well, I have seen Members of the House "play hurt." Members who were ill and dragged themselves to the airport to keep an important commitment back home.

I have seen Members with serious illness or disease struggle to do a good job, to make rollcall votes and committee meetings.

The picture of the Congress presented to the public via the Abcam scandal was not a fair one. This is not a place where you can reach in and pick any seven Members and expect that they will accept money in a brown paper bag. It is not that kind of place and it is an insult to all who have served well here that such a picture of the Congress be presented.

Scandal is what sells newspapers and soap on the evening news. Pay raises and debates over them in this body are in the same category. But these things do not begin to tell the story of what happens here on a day-to-day basis.

What happens here on a day-to-day basis is a struggle to get things done, to do the right thing for our districts, for the Nation and the world. What gets in the way of that is familiar to all of us.

The hectic schedule is a problem. The lack of predictability in the scheduling. The tug and pull of various people and interests wanting our attention. The seemingly constant attention to getting reelected. The accompanying preoccupation with raising money. And, of course, the impact that such a preoccupation has on policymaking.

There must be a movement developed to deal with these problems. I believe we should move to a 4-year term with a limit of three terms in the House and two 2-year terms in the Senate. I believe we should move to a 2-year budget and plug in a requirement that the Congress do meaningful oversight for 3 or 4 straight months each year.

Most importantly, we need campaign reform—a limit on PAC's, public financing, free access to media, and many other important changes. The

political system is being contaminated by money and we must do something about it.

Such dramatic changes must take place with pressure from the outside and I intend to do my share as a private citizen in that regard.

Being a private citizen again will not be altogether unhealthy. Getting out of politics for a time will give me an important perspective.

But there will never be anything to take the place of the warm friendships I have developed here. I have not had the chance to thank each of my colleagues and staff for their kindness. I hope this statement will at least partially serve that purpose.

WHITE-FROEB STUDY DISCREDITED BY SCIENTISTS

HON. L. H. FOUNTAIN

OF NORTH CAROLINA

IN THE HOUSE OF REPRESENTATIVES

Thursday, December 16, 1982

Mr. FOUNTAIN. Mr. Speaker, after 30 years of service to the people of the Second District of North Carolina, I am about to retire from the U.S. House of Representatives. Before leaving I would like to submit, for the Record, an item dealing with an issue with which I and many others have long been interested, namely, the alleged effect of smoking on the health of the nonsmoker.

Mr. Speaker, let me briefly place the issue into its proper context. In 1978, the Subcommittee on Tobacco of the House Committee on Agriculture heard testimony from a vast array of eminent scientists and physicians on the issue of the effect of tobacco smoke on nonsmokers. Those individuals who testified generally agreed that no conclusive scientific evidence exists to support the claim that smoking affects the health of nonsmokers. In 1980, however, an article appeared in the New England Journal of Medicine by Drs. White and Froeb entitled "Small Airways Dysfunction in Nonsmokers Chronically Exposed to Tobacco Smoke," in which the authors concluded that smoking in the workplace adversely affects the lung function of nonsmokers. This conclusion appeared to conflict with the testimony presented to the Subcommittee on Tobacco.

Since its publication, the White-Froeb study has been used to support both regulatory and legislative activities in the United States. For example, the study was referred to in testimony before the Civil Aeronautics Board during its recent consideration of rules regarding smoking aboard commercial aircraft. The National Research Council report entitled "Indoor Pollutants" which was issued in 1981 under an EPA contract also relies on the study. Finally, the White-Froeb study has received widespread attention in both State and local legislative and policymaking bodies.

The White-Froeb study continues to play an important role in legislative considerations, despite the fact that the study itself has been heavily criticized by scientists and health practitioners. Most recently, at the 1982 joint meeting of the American Lung Association-American Thoracic Society, Dr. Michael D. Lebowitz, professor of internal medicine, college of medicine, University of Arizona and special consultant to the Subcommittee on Tobacco, presented reasons why, in his own words, "the results of this study cannot be used to demonstrate an effect of passive smoking on forced expiratory flows in adults exposed in the workplace." Dr. Lebowitz, a noted specialist in epidemiology and respiratory diseases, said that the basic problem with the White-Froeb study is that it is "improperly designed" and that "there are problems with the whole data set and with the conclusion." Dr. Lebowitz also expressed concern that the significance of the White-Froeb data appeared to depend upon their unexplained omission of data from 3,000 subjects originally included in the study.

Mr. Speaker, Dr. Lebowitz wrote a letter, dated July 10, 1981, to our colleague, Congressman CHARLES ROSS, Chairman of the Tobacco and Peanut Subcommittee of the House Agriculture Committee, as a result of a personal interview which Chairman ROSS and Dr. Lebowitz had with Dr. White. With the personal consent of Chairman ROSS, I am inserting herewith Dr. Lebowitz's letter. It more fully explains the author's views regarding the White-Froeb study.

I also want to mention another evaluation of the White-Froeb study, one which was made by Dr. J. G. Gostomzyk, director of the department of health of the city of Augsburg, West Germany. After an extensive, detailed review of the White-Froeb study, Dr. Gostomzyk has concluded that the White-Froeb data were incompletely presented and did not satisfy the prerequisites for scientific credibility. In addition, Dr. Gostomzyk remarked that "Dr. White's methodology is not scientific but that of a lay person with convictions," and concluded that "we assume that Dr. White's study is an attempt at scientific validation of his credo and that he possibly is unaware of the inadequacy of this methodology." It is obvious that Dr. Gostomzyk is referring to Dr. White's outspoken antismoking activities in California, including Dr. White's endorsement of public smoking referendums which were, incidentally, twice rejected by the California voters.

Given these and other criticisms of the White-Froeb study, it would appear that the New England Journal of Medicine has, perhaps unwittingly, performed a disservice to its readership. It is extremely unfortunate that a study so fraught with methodological problems, as indicated through

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numerous criticisms by scientists in the United States and elsewhere, should have been published in such a reputable journal of medicine. The White-Froeb study should, therefore, not be relied upon by the Congress, Federal agencies, or other legislative or policymaking bodies when considering restrictions on smoking in public places.

THE UNIVERSITY OF ARIZONA

COLLEGE OF MEDICINE

Tucson, Ariz., July 10, 1982

Congressman CHARLES ROSE,
Chairman, Subcommittee on Tobacco and
Peonals, House of Representatives Ray-
burn Building, Washington, D.C.

DEAR CONGRESSMAN ROSE: The following is a summary of my notes on our visit to Dr. James White at UC San Diego, as per our discussion. Unfortunately, despite the statement in the editorial of the New England Journal of Medicine (27 March 1980), Dr. White and his co-author did not "faultlessly demonstrate a reduction in measures of small airways of healthy non-smokers exposed to cigarette smoke in the work place". It is apparent from our visit and the article that there were various faults in the present study, which shall be discussed.

The problems with the research design are as follows:

The participants were not only volunteers, but generally had to pay for the physical fitness course; this is the reason most were white-collar. Employees in specific factories invited White to run the physical fitness course in their factories as well, which would also bias the population sample. Blue-collar workers were not distributed randomly. (It has to be assumed that volunteers in the physical fitness courses fall into unrepresentative categories: the highly motivated, with an interest in health and usually healthier, those who are worried about health and generally less healthy; the first group would include fewer smokers and the second group would include more smokers.)

The questionnaire utilized was not a validated one per se; test-retest comparisons were made only on the smoking questions and very small groups of subjects. The smoking information was not validated. There were no test-retest or validations on symptoms asked in the questionnaire. The questionnaire itself was derived by the investigator, and included some questions from standard questionnaires; this did not appear to include standard respiratory questions, and in fact various typical respiratory questions (such as phlegm) were not asked. The questionnaire did not include questions on attitude, but did include questions on activity levels and jobs (duration, type). The questionnaire did ask how many smokers were in their work area, room size, and nature of the air conditioning. It also included questions about residences in the last 20 years (zip codes), so that exposures away from work were assessed by residential location. A question was asked about smokers in the home. (Thus, the smoking information is not validated, but is probably relatively accurate. The information about exposure to passive smoking is only approximate, as is the information on other occupational exposures. Exposures to air pollutants or to unknown toxic gases in the working place is only approximate, and their effects underestimated.)

Dr. White presented a paper to the American College of Sports Medicine, the abstract for which in 1977 indicated there were 7,122 subjects enrolled between 1969 and 1977. However, in the New England Journal of Medicine article, he states that the base

population analyzed is only 8,210 smokers and non-smokers enrolled between 1969 and 1979. Although he excluded all the ex-smokers, some whose zip codes were missing, his answers as to why the rest of the subjects were excluded were entirely unclear and tend to indicate potential bias in selection of subjects for consideration for analyses. It might be added that the 2,100 subjects analyzed in the NEJM article and those analyzed and presented in the Sports Medicine abstract appear to be the same as they yield exactly the same table of results (as determined from comparison of the table in the Sports Medicine manuscript and the NEJM table).

In addition to the sources of bias mentioned above, it is apparent that the non-smokers in clean work environments and those in smoking work environments have not only chosen not to smoke, but it is likely that those non-smokers working in smoking environments may be different for a variety of reasons from non-smokers working in clean environments. Furthermore, it is apparent that the non-smokers in non-smoking environments are quite different in that their lung function is "super normal" in comparison even with the Seventh Day Adventists (the source of the Morris prediction equations).

Dr. White did state that from the questionnaire and from the baseline tests that there were no significant differences in the three non-smoking/non-inhaling groups in terms of the amount of previous exercise or oxygen consumption, but he was unsure of the difference in percent of body fat. Smokers did have less body fat, were less in terms of having lower oxygen consumption, and had less activity. He says further that there were no differences between the groups in terms of childhood respiratory history (lower respiratory tract illnesses) from his submitted questionnaire information, but he did not ask about family history. He did not ask sufficiently about respiratory questionnaires to appropriately exclude groups on the bases of productive cough ("cough bronchitis"). He states that there were no differences in prevalence rates of questionnaire responses by zip codes; if so, this contradicts other evidence vis-a-vis the effects of air pollution in these areas. He was not able to assess other exposures such as those from hobbies, exposures to gas stoves, or transportation. In terms of passive smoking in the home, he excluded such passive smokers from the non-smoking and passive smoking groups, but not from any smoking groups. He was not able to provide any information about the distribution of characteristics in those eliminated from the original 7,000 or the 2,208 that qualified because of other questionnaire results.

With regards to the pulmonary function testing done by Dr. White, it must be first noted that the instrument used is not considered a satisfactory instrument in that it is non-linear (highly biased) at both high volumes and low volumes. (This has the effect of maximizing differences in that anyone with minor aberrations of total vital capacity or of flows at the end of the flow volume curve would have very different, that is, low, flows.) The comparisons that Dr. White did and reported on in his response letter in the NEJM (14 August 1980) would not in any way modify this opinion. Furthermore, Dr. White has the only pulmonary function technician and reader. Even though he was trained at the VA hospital and his techniques were evaluated by test-retest and by comparison to other readers, any biases inherent in Dr. White's thinking (see below) would affect the way he read the tests. Furthermore, he took the FEV₁ and flows off the same spirogram

using an approximation technique published by Morris, et al., which is not an adequate or accurate representation of those measures. All of his tests were baseline tests done after two and a half hours in the classroom in the evening on those without acute respiratory illnesses (usually on a Monday or Tuesday evening); thus, there is probably little diurnal variation or pretest biases other than those experienced by the workers during their work day and in their activities prior to the classroom. Although it is difficult to judge the effects of these factors, they may have influenced the test results, especially in those with any significant exposures during the day.

The major problem with the pulmonary function test results as reported is that they are not age- and height-adjusted, since lung volumes and flow rates are associated with both of these factors. In other words, Dr. White used raw values of flows and volumes to do comparisons. He did this on the assumption that the mean age and height were similar for the different groups. This is a mistake, since the distributions for those ages and heights could have differed. Furthermore, his quoted figures for percent predicted are strictly for the average person, age 40, with an average height, and does not represent the group for which they are provided. In terms of these statistical analysis, he just chose the SNK package among many. There is no correlation coefficient per se. "Normality" was not an objective of this study, so he cannot state anything about the normality of the subjects studied, including those he considered to have significantly different results from the non-exposed non-smokers. He does not understand the difference between clinical meaningfulness and statistical significance. It is quite obvious that the majority of those in the passive smoking and in the non-inhaling group are quite normal and that very few would be considered abnormal by any criteria.

In his reported results, he quotes as incorrect significance level of $p < .005$, whereas the level provided by the technique is $p < .05$. This is very different, given the number of comparisons made, and indicates that some of the results would not be significant if corrections were made for the number of comparisons. Furthermore, the data presented in Table 1 was used to recompute the SNK analysis by Mary C. Townsend, MPH (Department of Epidemiology, University of Pittsburgh). Those results differ from those published by Dr. White and are provided in the attachment. The most important of the differences is the finding that the passive smokers and light smokers differ for the male FEV₁ 75-85 percent. Thus, the effect of passive smoking on non-smokers is still unconfirmed, despite Dr. White's unfailing conviction that it is confirmed.

Other minor points: In terms of the carbon monoxide sampling, although it is stated that it was randomized, it was really on only 40 smoking and 40 non-smoking situations chosen by chance, but not by random selection. Dr. Froeb, the co-author with Dr. White, is a private practitioner in La Jolla and helped Dr. White in drafting the NEJM manuscript from the manuscript presented at the American College of Sport Medicine. It might be pointed out that San Diego is not strictly low in air pollution concentrations, nor uniformed throughout the area; this may bias some results. Dr. White performed the pulmonary function tests until "reproducible curves were obtained", but they do not necessarily follow the Intermountain, Snowbird, or ATS recommendations.

In reviewing Dr. White's response to the letter to the Editor in the NEJM (14 August 1980), it is quite clear that Dr. White did not satisfactorily answer all the questions raised, many of which are similar to those raised in this letter. It is questionable, from the discussion, whether Dr. White would pursue any further re-analysis of the data, nor necessarily could it be pursued. It is questionable, given the basic underlying problems in the research design, that re-analysis of the data would be worthwhile. On the other hand, given other results that contradict Dr. White's, including those now in press (such as Comstock et al., Johns Hopkins, presented at the Society for Epidemiological Research in June of 1981), it would be likely that a panel discussion of passive smoking might be valuable. I will be glad to furnish further discussion or help in that matter.

Sincerely,

MICHAEL D. LEDOWITZ, Ph.D.,
F.C.C.P.,
Professor of Internal Medicine.

TOM BUTTERFIELD

HON. IKE SKELTON

OF MISSOURI

IN THE HOUSE OF REPRESENTATIVES

Thursday, December 16, 1982

● Mr. SKELTON. Mr. Speaker, as 1982 draws to a close, it is customary to reflect upon the events of the past year. I would like to talk about an experience I had just over a year ago and about some sad news I heard just this week.

In December of 1981, a movie called, "The Children Nobody Wanted" was televised. This moving story depicted the work of a man named Tom Butterfield and the help he gave to fosterlings in Marshall, Mo. On Monday, December 13, my longtime friend, Tom Butterfield died of respiratory failure.

"The Children Nobody Wanted" is a true story. When Tom Butterfield was a freshman at Missouri Valley College in Marshall, Mo., he discovered the problems of children who have nowhere to go, and for whom the law makes few, if any, provisions. Boy by boy, he made a life for these homeless youngsters. Tom fought increasing odds, from the lack of money, to outdated laws. He became the youngest single adult—and the first bachelor—to be a legal foster parent in the State of Missouri. He and his boys rented an old country club and turned it into their ranch. Today, there are four ranches, giving a homelife to over 100 youngsters.

During this special time of the year, it is good to stop and think about the road we are traveling. Looking at the trail of Tom Butterfield's life, I can see that, although he died at the young age of 42, his contributions will go on for a very long time to come. It is appropriate, at this time of gift-giving, to look back at all the giving this man has done in his lifetime.

ADMINISTRATION'S INSENSITIVE APPROACH TO CANCER

HON. ALBERT GORE, JR.

OF TENNESSEE

IN THE HOUSE OF REPRESENTATIVES

Thursday, December 16, 1982

● Mr. GORE. Mr. Speaker, the present administration appears to be headed down a regulatory path that will needlessly expose millions of people to many known, cancer-causing chemicals at levels well beyond those traditionally accepted as safe and prudent. One example, documented in hearings held before the Investigations and Oversight Subcommittee of the Committee on Science and Technology which I chaired, was EPA's failure to take rapid action in setting reasonable limits for exposure to formaldehyde, although it is unquestionably an animal carcinogen. My colleague, Hon. GEORGE E. BROWN, Jr. has done some excellent work in this area and has found similar evidence of EPA's failure to regulate certain pesticides that have been clearly shown to cause tumors in animals. Two recent articles in the New York Times (Dec. 4, 1982) and the Baltimore Sun (Dec. 8, 1982) provide further documentation of the new, high-risk approach to Federal cancer policy. I commend them to the attention of my colleagues. It is time for us to halt this administration's crass and insensitive bottom-line approach in which costs to industry are balanced against increased human suffering. We all owe a debt of gratitude to the gentleman from California and I am looking forward to his forthcoming subcommittee report on this subject.

The articles follow:

(From the Baltimore Sun, Dec. 8, 1982)

EPA AND CANCER: THE SHIFTING STANDARDS
(By Ken Cook)

WASHINGTON.—In what some critics charge is a fundamental and unjustified change in Federal cancer policy, the Environmental Protection Agency (EPA) has determined that an insecticide which caused cancer in laboratory animals poses no cancer risk to human beings.

The decision removes the last barrier to the permanent registration of the insecticide permethrin for use on dozens of U.S. crops.

As a result of emergency exemptions granted by the agency since 1977, permethrin already is one of the country's major insecticides, used on millions of acres of vegetables, beans and cotton each year. Permethrin is marketed under the trade names Pounce and Ambush.

A leading critic of the EPA decision, Representative George E. Brown, Jr., (D., Calif.) characterizes the permethrin ruling as "one of several actions that suggest the EPA has adopted a new set of scientific principles in reaching regulatory decisions on proven animal carcinogens."

Federal pesticide law does not prohibit registration of cancer-causing chemicals if dietary and occupational exposure can be kept below the safety level established by the agency. By contrast, the Food and Drug Administration must by law prohibit the use

of any food additive shown to cause cancer in laboratory animals.

The practical effect of a decision to brand permethrin as a human carcinogen would have been a greater restriction on the number of crops for which it could be registered. Such a ruling might also have left the manufacturers, FMC Incorporated of Philadelphia, and ICI, a British firm, more vulnerable to product liability suits.

John W. Melone, director of EPA's hazard evaluation division and author of the permethrin decision (which appeared in the Federal Register in October), said that one of the long-term animal studies submitted by a manufacturer in support of the chemical's registration "was clearly positive" for cancer. It reported that tumors had appeared on mice after they had been fed permethrin over an extended period. Mr. Melone said five other studies submitted by manufacturers were accepted by EPA as showing no cancer-causing effects in laboratory animals. However, Mr. Melone described one of those studies as "quite controversial" because EPA scientists could not agree on the results. A seventh study, also conducted by a manufacturer, was rejected because of irregularities in the way it was conducted.

Mr. Melone described the permethrin case as "unique" for having so many long-term studies available for scrutiny by EPA scientists. Only two such studies normally are required for pesticide registration.

"We concluded that the weight of evidence suggested this chemical is highly unlikely to be a potential human oncogen (tumor-inducing substance)," Mr. Melone said in a telephone interview. "And since we have to make a decision, we believe permethrin should not be regulated as a potential human oncogen."

Regarding the permethrin ruling, Mr. Melone said, "There's no question it's a change in perspective."

Representative Brown, chairman of the House Subcommittee on (Agriculture) Department Operations, Research and Foreign Agriculture, which has jurisdiction over EPA's pesticide program, said that "for the agency to adopt a policy which, in effect, attempts to balance positive tests with negative ones is clearly a bold step."

Mr. Brown considers the action "a monumental and quasi-scientific leap of regulatory faith."

There is a continuing debate among cancer experts over how to weigh various types of evidence to determine a chemical's potential to cause cancer in humans. Although the precise mechanisms of cancer remain unknown, scientists have for some time agreed that proven animal carcinogens do not all pose an equal risk of cancer to humans. Traditionally, cancer regulatory decisions, including those made by EPA, have been made as if they did.

In the past few years, several cancer researchers and research institutions have proposed detailed systems by which regulatory agencies might distinguish between "strong" and "weak" carcinogens, based on information gained from long-term animal studies such as those submitted in the permethrin case. Regulatory actions might then take the form of an outright ban if such a system ranked the chemical as a strong cancer risk. Chemicals judged to be weak would be regulated less stringently, or not at all.

Last summer, EPA circulated to a select group of experts a draft of a proposal to modify the agency's original cancer policy guidelines promulgated in 1978. The draft proposed a ranking system similar to one developed by the International Agency for Re-

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3. Lenfant C, Liv BM. (Passive) smokers versus (voluntary) smokers. *N Engl J Med.* 1980; 302:742-3.

To the Editor: The observations of White and Froeb regarding the presence of small-airways dysfunction in passive smokers are quite important. Evidence that innocent bystanders may suffer physiologic changes in the airway bolsters the case for a ban on smoking in public areas much more than the simple observations of conjunctival irritation, bifactory offensiveness, and upper-airway distress. It therefore regret that their study is flawed by their use of the Dotti Pulmonary Performance Analyzer, a hot-wire flowmeter spirometer that fails to meet the technical recommendations of the American Thoracic Society.¹ Recently published evaluations of this spirometer show serious error in its measurement of forced vital capacity.² The accuracy of the forced mid-expiratory flow rate and forced end-expiratory flow rate used by White and Froeb to indicate small-airway function is predicated on accurate determination of the forced vital capacity.³ Unfortunately, the authors did not have access to this information regarding the inaccuracy of their spirometer when they did their studies. It is highly probable that the exceptionally large number of subjects in their study comprised cancels out individual errors in measurement. However, the relatively small differences between nonsmokers and passive smokers make this inaccuracy in their instrument a cause for concern. One hopes that their message and conclusions will soon be reinforced by other studies.

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To the Editor: The study by White and Froeb has a complicated design that involves a myriad of technical, medical, and behavioral variables. For example, several of the lung-function tests used in the study are controversial, particularly with respect to their importance in lung disease.¹ These tests can be influenced by numerous factors, including subject awareness, voluntary effort to perform the tests, the extent of a subject's physical training, the type of instrument used, the skill of the technician, the type of heating and cooking system in the home, the use of aerosol cosmetics, the use of medication, and the age and race of the subject. Research findings have shown also that there is great variability in the results of lung-function tests, especially in normal or asymptomatic subjects.^{2,3} In short, certain questions relating to the reported data need to be addressed before one can interpret this study.

Aside from any possible technical problems that the study may have, its experimental premise may be questionable. It is difficult to believe that the researchers have been able to identify a truly representative group of subjects who have work histories of 20 years or more but who have never been exposed to tobacco smoke. This "no exposure" group, along with other experimental groups in the study, needs verification from an epidemiologic point of view.

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To the Editor: Perhaps in the light of White and Froeb's finding of a physiologic mechanism for health hazards to adult passive smokers, medical workers will be inclined to pay more serious attention to the psychosocial consequences of the symptoms attendant on environmental pollution by tobacco smoke, as reported by nonsmokers. The range of symptoms includes eye and nasal irritations, coughing, impaired breathing, headache, drowsiness, dizziness, nausea, difficulty in staying alert, and interference with intellectual performance.⁴ Evidence of threats to physical health is important, but it is also important to study the possibility that smoke pollution interferes with the quality of life and efficiency in the carrying out of day-to-day activities, such as a student's ability to attend to a classroom lecture, a pilot's ability to operate an aircraft safely, or the ability of a person who finds cigarette smoke offensive to find a job. The concern over indexes of excess morbidity and mortality, although immensely important, is only one aspect of the problem.

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*Shor RE, Williams DC. Reported physiological and psychological symptoms of tobacco smoke pollution in nonsmoking and smoking college students. *J Psychol.* 1979; 101:203-18.

To the Editor: White and Froeb demonstrate the effect of 20 years of passive smoking in a working environment on pulmonary function and point out that the differences were significant only for FEF 25-75%. A study by the French Cooperative Group PAARC (Pollution atmosphérique et Affections respiratoires chroniques) looked at the effect of passive smoking in the home environment. The results support the conclusion that passive smoking has deleterious effects.

The study was conducted in eight towns throughout France; measurements of forced expiratory flow in persons 25 to 59 years of age were taken in their homes. The data from each household in which two adults (male and female) were examined were analyzed; 2812 wives who never smoked were studied in relation to the smoking habits of their husbands. The 1863 whose husbands did smoke had a significantly lower FEF 25-75%, but also a significantly lower FEV₁ and FVC, than wives whose husbands did not smoke (age-adjusted means were, respectively, 2.95 vs. 2.86 liters per second, $P = 0.03$; 2.60 vs. 2.55 liters, $P = 0.02$; and 3.17 vs. 3.12 liters, $P = 0.02$). This effect increased with the amount of tobacco passively smoked but became evident only in women 40 years of age or older, i.e., after about 15 years of exposure. When the sample was split into two groups (one of women younger than 40 years of age and the other of those 40 years old or older), it appeared that the differences were not significant before this age (age-adjusted means were, respectively, 3.20 vs. 3.19 liters per second for FEF 25-75%; 2.78 vs. 2.77 liters for FEV₁, and 3.36 vs. 3.35 liters for FVC). For women 40 years old or older, the differences became highly significant (age-adjusted means for FEF 25-75%, 2.73 vs. 2.59 liters per second, $P = 0.004$; for FEV₁, 2.43 vs. 2.35 liters, $P = 0.003$; and for FVC, 3.00 vs. 2.92 liters, $P = 0.006$). The differences persisted in all social classes and in the various towns studied. The differences observed for FEV₁ show that the reduction of pulmonary function due to passive smoking is important enough to be detected through such an "insensitive" test.

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: If prior pulmonary studies had not included passive smokers and exsmokers in their nonsmoker groups, they probably would have been able to differentiate between smokers and nonsmokers in their FEF 25-75% evaluations.

To compare a dose-response estimate with the results of our

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unable to provide a supply of matched blood in time. The systemic blood pressure had fallen to 60/40 mm Hg, the hematocrit was 10 per cent, blood-gas analyses showed the partial pressure of oxygen to be 68 mm Hg and of carbon dioxide to be 28.5 mm Hg, and the excess of base was 0.8 meq per liter.

We decided to administer the artificial blood to avoid serious anemic anoxia during the emergency surgery. The inspired oxygen concentration was 0.67 during nitrous oxide anesthesia. Initially, 500 ml of Fluosol was infused intravenously at a rate of 10 ml per minute, and systemic blood pressure rose to 100/60 mm Hg. A second infusion of 200 ml was administered, and shortly thereafter an additional 300 ml was given for a total of 1000 ml. The blood pressure rose further.

About two hours after the start of Fluosol therapy, the blood bank supplied 1300 ml of matched, citrated whole blood, which was infused intravenously while the operation was being completed.

The patient's general condition, including blood pressure, pulse rate, and blood-gas levels, was greatly improved by the infusion of Fluosol during surgery. Use of the blood substitute enabled us to go ahead with the operation.

Although Fluosol levels were not studied in this patient, the half-life in the blood has been shown to be nine days, and the washout time about three months, depending on the individual patient and the dose administered.¹ No toxicity attributable to the blood substitute was detected in this patient. We believe that further trial of Fluosol-DA as a blood replacement in emergency cases is justified.

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SMALL-AIRWAYS DYSFUNCTION IN PASSIVE SMOKERS

To the Editor: White and Froeb state in the March 27 issue that they found differences in mid-expiratory and end-expiratory flow (FEF 25-75% and FEF 75-85%) in their comparison of nonsmokers with passive smokers and smokers. This statement is remarkable since not all investigators who have used FEF 25-75% have been able to distinguish between smokers and nonsmokers,^{1,2} because only a limited number of smokers had abnormal test results.³ The dose-response relation found by Cuddeback et al.,⁴ indicated that the values for FEF 25-75% and FEF 75-85% were decreased in passive smokers by 13 per cent and 25 per cent, respectively, as compared with nonsmokers, whereas in heavy smokers these values were decreased by 19 and 35 per cent, respectively, as compared

with passive smokers. This relation existed despite the fact that the intake of total particulate matter by passive smokers is minimal in comparison to that of heavy smokers. Is it possible that passive smoking and smoking 40 cigarettes or more per day impair pulmonary function by nearly the same percentage? These findings are difficult to believe and require further investigation.

White and Froeb claim that their procedure is "generally agreed" on. Morris et al. view their data on FEF 75-85% much more skeptically and suggest that only values of less than 75 per cent of the predicted mean are present in a group of subjects who presumably have small-airways disease.⁵ The respective data for passive smokers reported in Table 1 of the article by White and Froeb are 85 per cent for women and 95 per cent for men.

The methods used by White and Froeb are open to criticism. Of course, FEF 25-75% and FEF 75-85% have proved to be more sensitive than forced vital capacity and forced expiratory volume in one second (FEV₁) in the ability to show dysfunction of the small airways. However, since the coefficient of variation for FEF 25-75% is three times larger than those for FVC and FEV₁, there is some doubt about whether the evidence of FEF 25-75% and FEF 75-85% is more conclusive than that of FVC and FEV₁.^{1,2,6}

The authors must have been faced with another difficult problem — the selection and grouping of the subjects. The information provided does not exclude the possibility of bias. To clarify this matter, a number of questions need to be answered. Why did the authors not mention the group of exsmokers who must certainly have existed in such a population sample? Why were nonsmokers who lived with a smoker not considered? Were the different occupations equally distributed among all subgroups? Such a distribution would not be in line with our experience. Were there no persons who moved from a working place where smoking was allowed to one where it was not, and vice versa?

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One can only strongly second the recommendation of Lenzani and Liu that the evidence must be corroborated and extended, and that the search for public policy on an issue of this importance must be based on "irrefutable scientific evidence."

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To the Editor: The study by White and Froeb has a complicated design that involves a myriad of technical, medical, and behavioral variables. For example, several of the lung-function tests used in the study are controversial, particularly with respect to their importance in lung disease.¹ These tests can be influenced by numerous factors, including subject awareness, voluntary effort to perform the tests, the extent of a subject's physical training, the type of instrument used, the skill of the technician, the type of heating and cooling system in the home, the use of aerosol cosmetics, the use of medication, and the age and race of the subject. Research findings have shown also that there is great variability in the results of lung-function tests, especially in normal or asymptomatic subjects.^{2,3} In short, certain questions relating to the reported data need to be addressed before one can interpret this study.

Aside from any possible technical problems that the study may have, its experimental premise may be questionable. It is difficult to believe that the researchers have been able to identify a truly representative group of subjects who have work histories of 20 years or more but who have never been exposed to tobacco smoke. This "no exposure" group, along with other experimental groups in the study, needs verification from an epidemiologic point of view.

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To the Editor: Perhaps in the light of White and Froeb's finding of a physiologic mechanism for health hazards to adult passive smokers, medical workers will be inclined to pay more serious attention to the psychosocial consequences of the symptoms attendant on environmental pollution by tobacco smoke, as reported by nonsmokers. The range of symptoms includes eye and nasal irritations, coughing, impaired breathing, headache, drowsiness, disinterest, nausea, difficulty in staying alert, and interference with intellectual performance.⁴ Evidence of threats to physical health is important, but it is also important to study the possibility that smoke pollution interferes with the quality of life and efficiency in the carrying out of day-to-day activities, such as a student's ability to attend to a classroom lecture, a pilot's ability to operate an aircraft safely, or the ability of a person who finds cigarette smoke offensive to find a job. The concern over indexes of excess morbidity and mortality, although immensely important, is only one aspect of the problem.

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*Sbor RE, Williams DC. Reported physiological and psychological symptoms of tobacco smoke pollution in nonsmoking and smoking college students. *J Psychol* 1979; 101:203-18.

To the Editor: White and Froeb demonstrate the effect of 20 years of passive smoking in a working environment on pulmonary function and point out that the differences were significant only for FEF 25-75%. A study by the French Cooperative Group PAARC (Pollution atmosphérique et Affections respiratoires chroniques) looked at the effect of passive smoking in the home environment. The results support the conclusion that passive smoking has deleterious effects.

The study was conducted in eight towns throughout France; measurements of forced expiratory flow in persons 25 to 59 years of age were taken in their homes. The data from each household in which two adults (male and female) were examined were analyzed; 2212 wives who never smoked were studied in relation to the smoking habits of their husbands. The 1863 whose husbands did smoke had a significantly lower FEF 25-75%, but also a significantly lower FEV₁ and FVC, than wives whose husbands did not smoke (age-adjusted means were, respectively, 2.95 vs. 2.86 liters per second, $P = 0.03$; 2.60 vs. 2.55 liters, $P = 0.02$; and 3.17 vs. 3.12 liters, $P = 0.02$). This effect increased with the amount of tobacco passively smoked but became evident only in women 40 years of age or older, i.e., after about 15 years of exposure. When the sample was split into two groups (one of women younger than 40 years of age and the other of those 40 years old or older), it appeared that the differences were not significant before this age (age-adjusted means were, respectively, 3.20 vs. 3.19 liters per second for FEF 25-75%; 2.78 vs. 2.77 liters for FEV₁, and 3.36 vs. 3.35 liters for FVC). For women 40 years old or older, the differences became highly significant (age-adjusted means for FEF 25-75%, 2.73 vs. 2.59 liters per second, $P = 0.004$, for FEV₁, 2.43 vs. 2.35 liters, $P = 0.003$; and for FVC, 3.00 vs. 2.92 liters, $P = 0.006$). The differences persisted in all social classes and in the various towns studied. The differences observed for FEV₁ show that the reduction of pulmonary function due to passive smoking is important enough to be detected through such an "insensitive" test.

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The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: If prior pulmonary studies had not included passive smokers and ex-smokers in their nonsmoker groups, they probably would have been able to differentiate between smokers and nonsmokers in their FEF 25-75% evaluations.

To compare a dose-response estimate with the results of our

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Comstock, G.W., Meyer, M.B., Helsing, K.J., Tockman, M.S.
"Respiratory Effects of Household Exposures to Tobacco Smoke and
Gas Cooking" Am Rev Resp Dis 124: 143-148, 1981.

SUMMARY: The records of 1,724 residents of Washington County, Maryland, who had participated in 2 studies of respiratory symptoms and ventilatory function were analyzed to evaluate the effects of exposures at home to tobacco smoke generated by other members of their households and to fumes from the use of gas as a cooking fuel. Currently smoking subjects showed the highest frequency of respiratory symptoms and impaired ventilatory function; former smokers showed a lower frequency of these findings; and persons who had never smoked had the lowest prevalence of abnormal respiratory findings. The presence of a smoker in the household other than the subject was not associated with the frequency of respiratory symptoms, and only suggestively associated with evidence of impaired ventilatory function. The use of gas for cooking was related to an increased frequency of respiratory symptoms and impaired ventilatory function among men, being most marked among men who had never smoked. There was no evidence that cooking with gas was harmful to women.

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Respiratory Effects of Household Exposures to Tobacco Smoke and Gas Cooking¹⁻³

GEORGE W. COMSTOCK, MARY B. MEYER, KNUD J. HELSING, and MELVYN S. TOCKMAN

Introduction

Domestic air pollution must have been a human health problem since the time that cave-dwelling hominids first built fires. Only recently, however, have such effects been documented. Smoke from fires in huts has been implicated as a cause of chronic respiratory disease both in India and in New Guinea (1, 2). In more modern homes, tobacco smoke produced by others, clearly an annoyance to many non-smokers, and fumes from cooking fuels are now coming under suspicion as causes of respiratory symptoms and reduced ventilatory function.

Both these sources of domestic air pollution have been shown to produce potentially damaging pollutants. Respirable particulates have been found to be higher in homes of smokers (3), and higher concentrations of nitrogen dioxide were recorded in homes where gas was used as a cooking fuel than in homes using electricity for cooking (4, 5). But the extent to which smoking by others or cooking with gas are detrimental to human health is a question that is still unsettled, largely because of the difficulties in measuring individual exposures and because of inconsistent findings.

Most of the subjects for studies of such exposures have been children. Studies using frequency of illnesses as an outcome measure agree that children from homes with smokers are more likely to have respiratory illnesses than those not exposed to tobacco smoke at home (6-14). Some doubt is cast on the specificity of this relationship, however, by findings that nonrespiratory illnesses were also more common among the children of smokers, although this excess could have occurred by chance (6, 8). Respiratory symptoms among children were reported by 4 studies, 3 finding an association with smoking by family adults (9, 15, 16), whereas one stated

SUMMARY The records of 1,724 residents of Washington County, Maryland, who had participated in 2 studies of respiratory symptoms and ventilatory function were analyzed to evaluate the effects of exposures at home to tobacco smoke generated by other members of their households and to fumes from the use of gas as a cooking fuel. Currently smoking subjects showed the highest frequency of respiratory symptoms and impaired ventilatory function; former smokers showed a lower frequency of these findings; and persons who had never smoked had the lowest prevalence of abnormal respiratory findings. The presence of a smoker in the household other than the subject was not associated with the frequency of respiratory symptoms, and only suggestively associated with evidence of impaired ventilatory function. The use of gas for cooking was related to an increased frequency of respiratory symptoms and impaired ventilatory function among men, being most marked among men who had never smoked. There was no evidence that cooking with gas was harmful to women.

AM REV RESPIR DIS 1981; 124:143-148

that no association was found but did not show the data on which this statement was based (17). Of 4 studies of ventilatory function (13, 16-18), 2 found an association with parental smoking (16, 18).

The effect of smoke produced by others, so-called involuntary smoking, on adults is even less clear. In Tucson, and in 3 small towns in the eastern United States, respiratory symptoms were not associated with exposure to tobacco smoke in the home (9, 17). The latter study found ventilatory function to be unrelated to involuntary smoking. In contrast, a third study of adults found evidence of airways obstruction among persons exposed to involuntary smoking at home (19).

There are also disagreements regarding the respiratory effects associated with gas cooking. In England and Scotland, and in 6 cities in the United States, children living in homes using gas for cooking were more likely to have had respiratory illnesses than those from homes using electricity (11-13). This association was not found in Columbus, Ohio, and in Long Island, New York (20, 21). Ventilatory function was found to be diminished among persons living in homes with gas cooking in 1 study (13) but not in 2 others (12, 20).

Whether or not domestic air pollution is hazardous to health is an issue

for preventive medicine and public health that needs to be resolved by additional and continued studies. The potential hazards of gas cooking and of involuntary smoking can both be controlled, the former by adequate stove ventilation (5) and the latter by providing additional incentives for smokers to quit and nonsmokers not to start. As energy-saving incentives increase, the potential importance of domestic air pollutants will also increase as home improvements decrease the dilution of household air by infiltration.

Methods

The subjects for this study were 1,950 adult residents of Washington County in western Maryland who were examined in 1977 in 2

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separate but related studies. One of these was a comparison of 3 standardized questionnaires: a respiratory questionnaire newly developed by the American Thoracic Society for the Division of Lung Diseases, National Heart, Lung and Blood Institute (22); the original version of the questionnaire used by the National Heart, Lung and Blood Institute (23); the 1976 version of the British Medical Research Council questionnaire (24). The 3 questionnaires were found to produce similar frequencies of histories of chronic cough and chronic phlegm. The new American Thoracic Society—Division of Lung Diseases questionnaire elicited more complaints of wheeze, whereas the older questionnaire used by the National Heart, Lung and Blood Institute elicited more mild breathlessness than the other 2 (25).

The 1,004 subjects for this questionnaire study were selected from the respondents to a health census of Washington County done in the summer of 1975 (25). Enumeration of residents is estimated to have been 89% complete. Selections of study subjects were made from the census lists in a way that produced samples of subjects for each of the 3 questionnaires that were similar in size and composition with respect to age, sex, race, rural residence, education, and cigarette smoking. Approximately three quarters of each sample were cigarette smokers. Although the selection process was too complex to allow definite statements as to representativeness, there was reason to believe that the subjects in each of the small subcategories of the samples did not differ from all enumerated residents in the same subcategories by more than chance variation.

The second group of 946 subjects were participants in a longitudinal study of white men who participated in a private census of Washington County in 1963 and who were 35 to 65 yr of age at that time (26, 27). Participation in that census was estimated to have been better than 98% complete. Subjects for the longitudinal study were selected to provide a representative sample of men who did and did not smoke cigarettes and who were residents of the county areas in and adjacent to the city of Hagerstown. All of the subjects in the longitudinal study were administered the new questionnaire developed by the American Thoracic Society.

The questionnaire study was done in the spring and summer of 1977. Approximately 40% of the subjects completed questionnaires that had been mailed to them; the others were interviewed by telephone. In the longitudinal study, all subjects were interviewed in person during the summer or autumn of 1977. Interviewers for both studies were carefully trained in the use of the questionnaires.

Ventilatory function testing was done in over half of the subjects in the questionnaire study and in virtually all of those in

the longitudinal study. Five satisfactory blows by the standing subject into a calibrated Stead-Wells spirometer were recorded (28). Both forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were calculated, as was the ratio of observed to predicted FEV₁. Corrections were made for temperature. For our analyses, only the best of the 5 values were used. Predicted values were calculated, using the data of Goldman and Becklake (29), to adjust for age, sex, and height.

Household exposures were assessed from information recorded in the health census of 1975. Information was available on smoking histories of adult household members, the use of gas as a cooking fuel, air conditioning, the number of adults and children in the household, and the number of rooms. Several calculated indexes were used: persons per room, children under 15 yr of age per household, ever-smokers per room and per household, and current cigarette smokers per household. Years of school completed and number of bathrooms in the household were used as indicators of socioeconomic status.

Six groups were selected for final analysis. Their derivation from the 1,950 subjects in the 2 original studies is shown in a flow diagram (figure 1). Most of the exclusions occurred among longitudinal study participants, 15% of whom were not identified in the 1975 census. Some households contained 2 index persons. Because of their small number, the simplest method of handling this potential problem was to exclude them from the analysis. Another small group of persons was dropped because of incomplete information on their respiratory questionnaires, virtually all involving mailed questionnaires. The final 6 study groups consisted of 426 men and 113

women who had never smoked cigarettes, 199 men and 33 women who had formerly smoked cigarettes, and 644 men and 309 women who currently smoked cigarettes.

To adjust findings for the effects of potentially confounding factors, binary variable multiple regression was used, as described by Feldstein (30) and adapted for epidemiologic use by Shah and Abbey (31). This regression method does not assume that relationships are linear and minimizes the effect of extreme values. It does assume that the contributions of the independent variables are additive.

Results

Characteristics of the subjects in the 6 study groups are shown in table 1. Differences in distribution of characteristics between men and women resulted largely from the fact that the males represented 2 study populations with different criteria for selection, since the longitudinal study involved only men, while the questionnaire study population was composed of nearly equal numbers of each sex. Differences between persons who never smoked, former cigarette smokers, and current cigarette smokers also reflected differences between the kinds of persons who selected themselves into these 3 smoking categories. The distribution of current smokers by amount smoked was caused in part by over-sampling heavy smokers for the questionnaire study. Because of the resulting differences between the study groups, their experiences were analyzed separately as proportions of persons

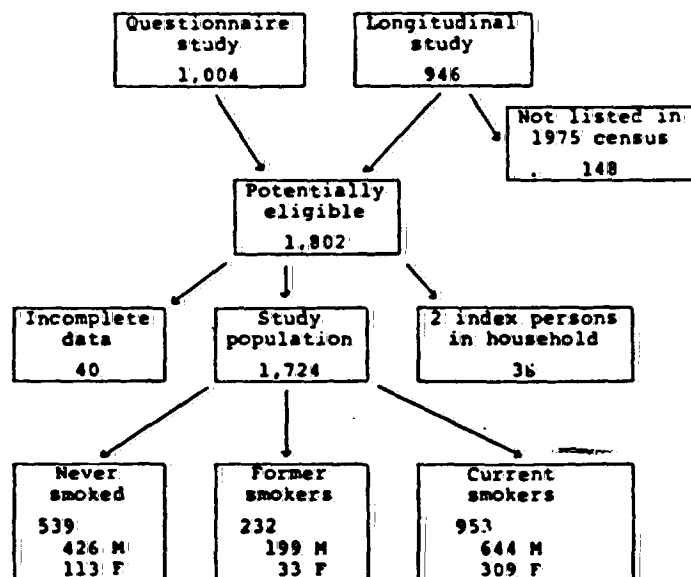


Fig 1. Derivation of study populations

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TABLE 1
PERCENTAGE DISTRIBUTION OF SUBJECTS IN STUDY GROUPS BY SEX, CIGARETTE SMOKING HISTORY,
AND OTHER SELECTED CHARACTERISTICS

Characteristics		Men			Women		
		Never Smoked	Exsmokers	Current Smokers	Never Smoked	Exsmokers	Current Smokers
Number of subjects		426	199	644	113	33	309
Age in 1975	20-34	8.2	5.0	15.5	35.4	33.3	35.6
	35-44	9.2	7.5	15.1	23.9	12.1	29.1
	45-54	34.5	38.2	42.2	31.0	27.3	25.6
	55-64	31.9	32.2	22.4	9.7	27.3	9.7
	65+	16.2	17.1	4.8	0	0	0
Education	< 12	30.3	53.3	46.6	48.6	27.3	51.8
	12	31.7	25.6	33.1	31.9	45.5	27.8
	> 12	38.0	21.1	20.3	19.5	27.3	20.4
Number of bathrooms	1 or less	54.2	69.3	71.0	73.5	57.6	69.9
	> 1	45.8	30.7	29.0	26.5	42.4	30.1
Persons/room	< 0.5	48.1	44.7	37.3	27.4	36.4	27.8
	> 0.5	51.9	55.3	62.7	72.6	63.6	72.2
Children < 15	0	68.5	74.9	57.5	45.1	45.5	39.5
	1+	31.5	25.1	42.5	54.9	54.5	60.5
Air conditioning	Yes	67.1	65.3	59.2	54.9	57.6	59.9
	No	32.9	34.7	40.8	45.1	42.4	40.1
Current number of cigarettes/day	0	100.0	100.0	0	100.0	100.0	0
	< 20/day	0	0	20.7	0	0	35.6
	20+ /day	0	0	79.3	0	0	64.4
Other cigarette smokers in household	No	77.7	62.3	46.1	68.1	39.4	37.9
	Yes	22.3	37.7	53.9	31.9	60.6	62.1
Cooking fuel	Electricity	74.8	63.8	65.0	62.8	69.7	61.2
	Gas	16.0	29.1	28.9	29.2	27.3	33.6
	Other	9.2	7.0	6.1	8.0	3.0	5.2

with respiratory findings, adjusted for the effects of independent variables shown in table 1.

Effect of other smokers in household. The frequency of major respiratory symptoms among subjects showed little evidence of an association with the presence of some one else in the household who smoked cigarettes (table 2). This held true regardless of sex or smoking history of the subjects. None of the relative risks nor the proportion of relative risks greater than 1.0 exceeded what could easily have resulted from chance. The presence of poor ventilatory function, defined as FEV₁ being less than 80% of the predicted value or less than 70% of the FVC, is shown in table 3. Although there is a definite tendency for persons with another smoker in the household to have impaired ventilatory function, none of the observed differences was great enough to achieve significance.

Effect of cooking fuel. The associations of respiratory symptoms with the type of fuel used for cooking are shown in table 4, again as adjusted proportions. Relative risks are shown for the comparisons of gas with electricity. Men whose households had gas

as a cooking fuel were at greater risk of having each of the respiratory symptoms than men whose households used electricity as a cooking fuel, although these risks achieved significance ($p < 0.05$) only for chronic cough, wheeze, and breathlessness of Grade 3 or more among men who never smoked. Among women, there was no evidence that exposure to gas cooking was associated with a greater risk of having respiratory symptoms than exposure to other cooking fuels. If a crude correction for multiple comparisons is made by multiplying p values by 24 (the total number of comparisons, counting cough and phlegm as one comparison because of their high correlation), only the excess risk of breathlessness of Grade 3 or more among men who never smoked cigarettes retains significance at a p value of 0.05 or less.

The adjusted proportions of persons with impaired ventilatory function as related to cooking fuel is shown in table 5. Among men who never smoked cigarettes, gas cooking was definitely associated with impaired ventilatory function, even when corrected for multiple comparisons. There were too few women who had never smoked ciga-

rettes and whose ventilatory function was tested to put any reliance in the similar association observed among them for gas cooking and diminished FEV₁. There was only slight evidence of an association of impaired ventilatory function associated with gas cooking among men who formerly smoked cigarettes, and none among men or women who currently smoked cigarettes.

Discussion

The importance of indoor sources of air pollution, such as tobacco smoke and fumes from unvented gas flames, is almost certain to increase as homes are made more and more air-tight in an effort to hold down heating and cooling costs. Although the evidence of harm from passive smoking or gas cooking is not yet conclusive, it is sufficiently suggestive among children to warrant serious consideration. Part of the difficulty in establishing an association between household exposures and respiratory symptoms among adults is that they have a variety of exposures outside of the home, such as air pollutants in the community or at work,

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TABLE 2
ADJUSTED PERCENTAGES* OF PERSONS WITH SPECIFIED RESPIRATORY SYMPTOMS BY SEX AND NUMBER OF CIGARETTE SMOKERS IN THE HOUSEHOLD EXCLUSIVE OF SUBJECTS, AND BY CIGARETTE SMOKING HISTORY.

	Number of Cigarette Smokers in Household Exclusive of Subjects					
	Men			Women		
	0	1+	RR†	0	1+	RR†
Never Smokers						
Number	331	95	—	77	36	—
% with respiratory symptoms:						
Chronic cough	8.3	8.0	0.96	6.0	1.0	0.17
Chronic phlegm	8.4	7.6	0.90	5.8	4.2	0.72
Chronic cough and phlegm	3.7	4.8	1.30	4.6	1.3	0.28
Wheeze	22.1	23.0	1.04	20.1	29.1	1.45
Breathlessness, grade 3	3.9	4.2	1.08	8.5	15.2	1.79
Chest illness in past 3 yr	12.0	11.0	0.92	24.2	23.3	0.96
Exsmokers						
Number	124	75	—	13	20	—
% with respiratory symptoms:						
Chronic cough	12.6	16.4	1.3	15.3	10.0	0.7
Chronic phlegm	13.7	21.3	1.6	8.8	9.3	1.1
Chronic cough and phlegm	7.6	14.1	1.9	8.8	9.3	1.1
Wheeze	38.0	49.1	1.3	7.4	25.2	3.4
Breathlessness, grade 3	12.2	15.8	1.3	3.3	17.9	5.4
Chest illness in past 3 yr	20.5	24.8	1.2	44.8	30.9	0.7
Current Smokers						
Number	297	347	—	117	192	—
% with respiratory symptoms:						
Chronic cough	39.4	35.2	0.89	27.9	33.0	1.18
Chronic phlegm	34.9	31.2	0.89	28.2	30.2	1.07
Chronic cough and phlegm	24.2	24.5	1.01	18.2	22.7	1.25
Wheeze	54.0	48.4	0.90	50.2	48.6	0.97
Breathlessness, grade 3	19.4	15.1	0.78	16.1	24.5	1.52
Chest illness in past 3 yr	18.1	14.8	0.82	27.3	30.8	1.13

* Adjusted for effects of characteristics in table 1 except for presence of other smokers in household.

† Relative risk associated with having a cigarette smoker other than the subject in the household.

TABLE 3
ADJUSTED PERCENTAGES* OF PERSONS WITH SPECIFIED DEGREES OF VENTILATORY FUNCTIONS BY SEX AND NUMBER OF CIGARETTE SMOKERS IN THE HOUSEHOLD EXCLUSIVE OF SUBJECTS, AND BY CIGARETTE SMOKING HISTORY.

	Number of Cigarette Smokers in Household Exclusive of Subjects					
	Men			Women		
	0	1+	RR†	0	1+	RR†
Never Smokers						
Number	291	78	—	34	15	—
% with impaired ventilatory function:						
FEV ₁ <80% predicted	5.0	7.1	1.42	8.9	0	0
FEV ₁ /FVC <70%	7.8	9.3	1.19	0	0	—
Exsmokers						
Number	114	65	—	7	10	—
% with impaired ventilatory function:						
FEV ₁ <80% predicted	9.2	16.1	1.8	0	0	—
FEV ₁ /FVC <70%	18.1	20.6	1.1	0	0	—
Current Smokers						
Number	215	257	—	49	93	—
% with impaired ventilatory function:						
FEV ₁ <80% predicted	22.8	26.1	1.14	15.8	17.5	1.11
FEV ₁ /FVC <70%	27.2	30.1	1.11	7.7	9.9	1.29

* Adjusted for effects of characteristics in table 1 except for presence of other smokers in household.

† Relative risk associated with having a cigarette smoker other than the subject in the household.

or associations with smokers in many places away from home.

Furthermore, it seems likely that an effect of household exposures will be demonstrable only among persons who have never smoked. The exposures from one's own smoking, particularly from inhaling the smoke, are many times more intense than would be tolerated in the ambient air. In the present study, as in many others, current smokers had much higher rates of respiratory symptoms than persons who had never smoked. Former cigarette smokers had rates intermediate between persons who had never smoked and current smokers, perhaps because the presence of these symptoms had induced them to stop smoking. In any case, these findings among former smokers emphasized the need to base studies of household exposures on persons who have never smoked rather than on persons who are not current smokers, a group that is a mixture of those who have never smoked and those who have quit.

The present study also suggested that effects of household exposures may be more readily demonstrable among men than among women. At first glance, this seems paradoxical, since women in this community are much less likely to work outside of the home than men, and hence are presumably more likely to be exposed to pollutants at home. But domestic air pollution is nothing new, dating back at least to the times of the cave-dwelling Cro-Magnon people. Judging from present day experiences in India and New Guinea (1, 2), smoke exposure in the home probably did not diminish greatly until stoves and furnaces came into common use only a few hundred years ago. Selective factors for resistance to smoke have thus had ample time to operate, and it seems possible that this selection might have resulted in women being less susceptible to domestic smoke and fumes than men. Whatever the reason, recent reports have indicated that deterioration in ventilatory function among cigarette smokers is less marked among women than among men (32, 33). It is also pertinent to note that one of the studies that failed to find an effect of gas cooking on adults was limited to women (20).

Because of the contradictory findings thus far reported, it is clearly desirable to look further at the prob-

TABLE 4.
ADJUSTED PERCENTAGES* OF PERSONS WITH SPECIFIED RESPIRATORY SYMPTOMS BY SEX AND TYPE OF COOKING FUEL AT HOME, AND BY CIGARETTE SMOKING HISTORY.

	Men				Women			
	Gas	Elec.	Other	RR†	Gas	Elec.	Other	RR†
Never Smokers								
Number	68	319	39	—	33	71	9	—
% with respiratory symptoms								
Chronic cough	16.1	6.6	7.2	2.44‡	8.3	3.7	0	2.24
Chronic phlegm	10.3	8.2	5.0	1.26	4.8	6.5	0	0.74
Chronic cough and phlegm	8.7	3.1	2.8	2.81	5.2	3.7	0	1.41
Wheeze	33.9	20.0	20.8	1.70‡	29.4	21.8	9.4	1.35
Breathlessness, grade 3	11.2	2.6	2.6	4.31‡	0.2	16.7	0.7	0.01‡
Chest illness in past 3 yr	16.3	11.0	9.7	1.48	8.6	29.0	39.7	0.30‡
Exsmokers								
Number	58	127	14	—	9	23	1	—
% with respiratory symptoms								
Chronic cough	20.9	11.7	7.5	1.79	23.3	7.8	10.9	2.97
Chronic phlegm	24.8	13.7	8.6	1.81	20.0	4.9	6.5	4.08
Chronic cough and phlegm	14.9	8.0	8.6	1.87	20.0	4.9	6.5	4.08
Wheeze	52.9	40.1	18.8	1.32	14.6	20.1	5.5	0.72
Breathlessness, grade 3	18.6	11.2	14.3	1.66	16.5	11.1	0	1.48
Chest illness in past 3 yr	22.7	22.5	16.3	1.01	59.8	25.4	76.4	2.35
Current Smokers								
Number	186	419	39	—	104	189	16	—
% with respiratory symptoms								
Chronic cough	42.5	34.5	39.5	1.23	28.9	32.2	32.3	0.89
Chronic phlegm	36.7	32.5	20.5	1.13	32.3	27.0	39.6	1.20
Chronic cough and phlegm	29.1	23.2	15.1	1.25	24.1	18.3	33.1	1.32
Wheeze	51.9	50.6	50.5	1.03	52.5	46.4	60.7	1.13
Breathlessness, grade 3	18.4	17.3	8.1	1.06	27.9	17.7	22.8	1.58
Chest illness in past 3 yr	17.1	16.1	14.6	1.06	26.2	30.4	39.1	0.86

* Adjusted for effects of characteristics shown in table 1 except for cooking fuel.

† Relative risk associated with gas compared to electricity as cooking fuel.

‡ $p < 0.05$.

lem of household exposures. The specificity of the associations of respiratory findings with these exposures should be investigated to help rule out the possibility that exposed populations have other factors that cause them to have more illness in general or lead them to seek medical care more readily than the unexposed. Findings should also be reported separately for each sex, and for at least 3 groups of smokers—never, former,

TABLE 5.
ADJUSTED PERCENTAGES* OF PERSONS WITH SPECIFIED DEGREES OF VENTILATORY FUNCTION BY SEX AND TYPE OF COOKING FUEL AT HOME, AND BY CIGARETTE SMOKING HISTORY.

	Men				Women			
	Gas	Elec.	Other	RR†	Gas	Elec.	Other	RR†
Never Smokers								
Number	55	281	33	—	10	33	6	—
% with:								
FEV ₁ < 80% predicted	16.4	3.9	0.4	4.21‡	14.4	5.4	0	2.67
FEV ₁ /FVC < 70%	21.9	5.6	6.8	3.91‡	0	0	0	—
Exsmokers								
Number	53	113	13	—	5	11	1	—
% with:								
FEV ₁ < 80% predicted	17.9	9.0	10.7	1.99	0	0	0	—
FEV ₁ /FVC < 70%	23.1	18.0	10.8	1.29	0	0	0	—
Current Smokers								
Number	123	320	28	—	42	93	7	—
% with:								
FEV ₁ < 80% predicted	24.9	25.9	8.9	0.96	13.2	18.7	14.6	0.71
FEV ₁ /FVC < 70%	32.4	29.6	4.9	1.09	10.8	9.4	0	1.29

* Adjusted for effects of characteristics in table 1 except for cooking fuel.

† Relative risk associated with gas compared to electricity as cooking fuel.

‡ $p < 0.001$.

and current. Adjusting for these factors may obscure a real association in one of the subgroups. Exposures outside the home should also be taken into account whenever possible.

An additional incentive for establishing whether or not household exposures to tobacco smoke and gas cooking are important is that both are remediable. Venting gas stoves can markedly reduce concentrations of oxides of nitrogen in the home (5). The possibility that smoking may harm others, especially children, should increase motivation for smokers to quit and nonsmokers not to start. Perhaps the Victorian custom of smokers retiring to a specified room to indulge their habit should be reinstituted, particularly if that space can also be vented to the outside.

Acknowledgment

The writers wish to thank Louise Doucette, Roseann McTyre, and Pearl Van Natta for statistical assistance, and Kathleen Trumppower for typing the manuscript.

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Kauffmann, F., Tessier, J.F., Oriol, P. "Adult Passive Smoking In The Home Environment: A Risk Factor For Chronic Airflow Limitation" American Journal of Epidemiology 117: 269-280, 1983.

SUMMARY: Using the data of the French Cooperative Study PAARC (Pollution Atmospherique et Affections Respiratoires Chroniques), which in 1975 surveyed more than 7800 adult residents of seven cities throughout France, the authors compared the spirometric measurements of two groups of nonsmokers: those with and without exposure to passive smoking in the home. They restricted the analysis to subjects aged 40 years or [sic] more (i.e., those presumably exposed for 15 years or more to smoking by their spouses) and who were living in households without other persons aged 18 years or older (to avoid potential misclassification as true nonsmokers of persons living with non-interviewed individuals). The authors found that nonsmoking subjects of either sex whose spouses were current smokers of at least 10 g of tobacco a day had significantly lower forced mid-expiratory flow rate (FEF 25-75) than those married to nonsmokers. This difference was not explained by social class, educational level, air pollution, or family size. Women, among whom passive smoking is much more prevalent than it is among men, also showed a significant difference in forced expiratory volume in one second (FEV1), and a clear dose-effect relationship to amount of smoking by their husbands was found in the large subgroup of women without paid work (i.e., those not exposed to workplace smoking).

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ADULT PASSIVE SMOKING IN THE HOME ENVIRONMENT: A RISK FACTOR FOR CHRONIC AIRFLOW LIMITATION

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Kauffmann, F. (INSERM U. 169, F-94807 Villejuif Cedex, France), J-F. Tessier and P. Oriol. Adult passive smoking in the home environment: a risk factor for chronic airflow limitation. *Am J Epidemiol* 1983;117:269-80.

Using the data of the French Cooperative Study PAARC (Pollution Atmosphérique et Affections Respiratoires Chroniques), which in 1975 surveyed more than 7800 adult residents of seven cities throughout France, the authors compared the spirometric measurements of two groups of nonsmokers: those with and without exposure to passive smoking in the home. They restricted the analysis to subjects aged 40 years or more (i.e., those presumably exposed for 15 years or more to smoking by their spouses) and who were living in households without other persons aged 18 years or older (to avoid potential misclassification as true nonsmokers of persons living with non-interviewed individuals). The authors found that nonsmoking subjects of either sex whose spouses were current smokers of at least 10 g of tobacco a day had significantly lower forced mid-expiratory flow rate (FEF₂₅₋₇₅) than those married to nonsmokers. This difference was not explained by social class, educational level, air pollution, or family size. Women, among whom passive smoking is much more prevalent than it is among men, also showed a significant difference in forced expiratory volume in one second (FEV₁), and a clear dose-effect relationship to amount of smoking by their husbands was found in the large subgroup of women without paid work (i.e., those not exposed to workplace smoking).

airway obstruction; educational status; epidemiologic methods; smoking; social class; spirometry

Active smoking is well recognized as a risk factor for chronic airflow limitation (1). The role of passive smoking has not yet been finally defined. One study (2) re-

cently demonstrated the deleterious effect for nonsmokers of working in a smoky environment for 20 years, whereas two studies (3, 4) did not show a significant

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Abbreviations: BMRC, British Medical Research Council; ECSC, European Coal and Steel Community; FEF₂₅₋₇₅, forced mid-expiratory flow between 25 and 75 per cent of vital capacity; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PAARC, Pollution Atmosphérique et Affections Respiratoires Chroniques.

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decrease in forced expiratory volume with household exposure to tobacco smoke in adults, though a trend was found in one study (4).

We present here a detailed analysis of lung function indices among adults according to passive smoking in the home. Confounding factors and dose-effect relationships are considered.

MATERIALS AND METHODS

The detailed protocol of the French Cooperative Study PAARC (Pollution Atmosphérique et Affections Respiratoires Chroniques) realized in 1975 has been published elsewhere (5). The primary purpose of the study was to look at the possible role of air pollution on respiratory symptoms and ventilatory function. The effect was hypothesized as small and therefore, the design of the study took into account various confounding variables and included a large number of subjects. This provides a good opportunity to look at the possible role of passive smoking. Briefly, the adult subjects for this study were 23,715 residents of 24 areas in seven cities throughout France (Bordeaux, Lille, Lyons, Mantes-la-Jolie, Marseilles, Rouen, and Toulouse). These subjects, all 25-59 years of age, were members of households selected by a preliminary survey, and were all French, non-manual employed "heads" of household (to avoid subjects with important occupational exposure), and resident in the area for at least three years (to have a known exposure to air pollution for a minimal duration). In the main survey, 6 per cent of the subjects selected refused and 7 per cent were not seen for other reasons. The remaining 87 per cent were interviewed at home with a questionnaire derived from the British Medical Research Council/European Coal and Steel Community questionnaire (BMRC/ECSC) (5, 6). Respiratory symptoms, past and present personal smoking habits, occupational exposure, occupation, social

class, educational level, composition of the household, and housing conditions were recorded.

Spirometric measurements with a dry expirograph (Vitalograph) were obtained for 95 per cent of the interviewed. At least three tracings were performed following ECSC recommendations (7). The maximum values of forced vital capacity (FVC), and of forced expiratory volume in one second (FEV_1) expressed in ambient temperature and pressure saturated conditions were used in analysis. Forced mid-expiratory flow between 25 and 75 per cent of the vital capacity (FEF_{25-75}) was calculated on the tracing with the maximum FEV_1 . Good tracings were defined by standard criteria. Although a pilot study had previously been undertaken on 3000 individuals (5), there remained some discrepancies in the data between towns in the main study, in particular, the percentage of poor tracings and regression coefficients on age were significantly different between towns. Because of this, to avoid possible bias, we considered in the analysis town-adjusted spirometric variables. For the 6707 men and 8287 women with good tracings, we calculated the regressions of FVC, FEV_1 , and FEF_{25-75} on age and height for each sex and town and then adjusted normalized spirometric variables for age, height, sex, and town. Normalized value of FVC for a given sex of a subject living in town i = (observed FVC - (a_i Age + b_i Height + c_i)) / $\sqrt{s_i^2}$, where a_i and b_i are the regression coefficients on age and height, c_i the intercept and s_i^2 the residual variance for town i . Because the main analysis is restricted to subjects 40 years of age or more, for a reason to become apparent, we then used regressions restricted to people of this age group for a better adjustment, though using the general regression would not change the figures much. In the presentation, the normalized values were converted to those for subjects of mean age and height.

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Adjusted FVC = $\overline{\text{FVC}} + \text{normalized FVC}$

$$\times \sqrt{\frac{\sum_i (n_i - 1)s_i^2}{\sum_i (n_i - 1)}}$$

where n_i is the number of subjects avail-
able for regression in town i and $\overline{\text{FVC}}$ the
mean among all subjects of the same sex.

Current smokers were divided into
heavy smokers (20 g or more of tobacco a
day, as cigarettes, cigars, or pipe), moder-
ate smokers (10–19 g a day) and light
smokers (up to 9 g a day). Ex-smokers
were those who had stopped for at least one
month. The usual nonsmokers were di-
vided into "true" nonsmokers, defined as
those living in households with no smoker
or ex-smoker interviewed, and passive
smokers, those living with at least one
smoker or ex-smoker. In the present
analysis, we considered mainly those liv-
ing with a current smoker of 10 g a day or
more. Unless otherwise specified, it is this
group which is called passive smokers.
Occasionally, light passive smokers, i.e.,
nonsmokers living with a current smoker
of 1–9 g a day are considered. Those liv-

ing with an ex-smoker are excluded from
the analysis of passive smoking.

We restricted the analysis to the
homogeneous group of 5266 households
with two spouses interviewed and living
with no other person aged 18 years or
more to avoid potential misclassification
as true nonsmokers of persons previously
living with a smoking spouse or living
with a son or daughter aged 18–24 years
not interviewed or living with a spouse 60
years or older not interviewed. The active
and passive smoking of the 7818 house-
hold members who performed good spirometric
tracings are presented in table 1.
Men were 2.6 times more often active
smokers than women and among non-
smokers in the usual sense (i.e., nonactive
smokers), women were 5.2 times as likely
to live with a spouse who was a current
smoker than men were.

Based on their most recent occupation,
subjects were classified according to
French sociooccupational classes defined
by the Institut National de la Statistique
et des Etudes Economiques. Classes III,
IV, II, V, VI, VII, IX were represented in
the study and this order corresponds

TABLE 1
Active and passive smoking among adult residents of seven cities throughout France, surveyed in the
French Cooperative Study PAARC*

	Men	Women
Total	3915	3903
Ever-smokers (active)		
Smokers ≥ 20 g/day	1103	189
Smokers 10–19 g/day	656	254
Smokers 1–9 g/day	466	406
Ex-smokers	638	252
Passive smokers		
Living with a smoker ≥ 20 g/day	27	710
Living with a smoker 10–19 g/day	38	448
Living with a smoker 1–9 g/day†	56	322
Living with an ex-smoker	44	461
True nonsmokers	849	826
Smoking habits unknown	38	35

* Pollution Atmosphérique et Affections Respiratoires Chroniques.

† Referred to later as passive smokers.

‡ Referred to later as light passive smokers.

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roughly to British social classes I; II; III; III; III, IV or V; III or IV; undefined. More precisely, they represent the following occupations (in parentheses are given the percentages observed for men and women, respectively): III (27 and 8 per cent), managers, administrators, professionals; IV (31 and 16 per cent), intermediate—teachers, technicians, nurses, administrators; II (16 and 8 per cent), self-employed—shopkeepers, craftsmen; V (22 and 29 per cent), employees—clerks, salespersons; VII (0.4 and 8 per cent), manual workers, employed; VII (3 and 5 per cent), personal service workers; IX (0.2 and 26 per cent), never employed. Subjects were classified in three groups by educational level: persons having completed the primary level (45 per cent of men and 52 per cent of women), secondary level (30 and 35 per cent) and university degree (25 and 13 per cent).

Using the means of daily measurements over a three-year period of SO_2 (acidimetric method), which was the only pollutant measured that was found to be related to ventilatory function (8), subjects were classified as living in areas of low pollution ($\text{SO}_2 < 50 \mu\text{g}/\text{m}^3$), moderate pollution ($50 \mu\text{g}/\text{m}^3 \leq \text{SO}_2 < 100 \mu\text{g}/\text{m}^3$) and heavy pollution ($\text{SO}_2 \geq 100 \mu\text{g}/\text{m}^3$).

Chi-square tests and analysis of variance with calculations of adjusted percentages (Cochran's method) and adjusted

means (analysis of variance and multiple regression) were used (9, 10).

RESULTS

Comparing true nonsmokers and passive smokers in the whole sample, FEV_1 and FEF_{25-75} showed opposite trends in men, and indicated that women had slightly lower values of FVC, FEV_1 , and FEF_{25-75} for passive smokers than true nonsmokers, but the differences were not significant (table 2). Going back to crude FEF_{25-75} values according to age for women, it appears that a difference between true nonsmokers and passive smokers began around age 40 years (figure 1). This is not surprising because the younger subjects have presumably been exposed for a relatively short time. Restricting the comparison to subjects aged 40 years or more, i.e., presumably exposed for 15 years or more (table 3), the difference in FEF_{25-75} became significant for both men and women. FEV_1 was significantly lower only for women passive smokers, but for men, a trend in the same direction was observed. From these results, it appears that living for at least 15 years with a current smoker of 10 g/day or more was associated with a lower FEF_{25-75} and to a lesser extent with a lower FEV_1 .

We then looked to see if these differences might be explained by confounding

TABLE 2
FVC, FEV_1 , and FEF_{25-75} (mean \pm SD) according to passive smoking among adult residents of seven cities throughout France, surveyed in the French Cooperative Study PAARC

	Men			Women		
	True nonsmokers	Passive smokers	p value	True nonsmokers	Passive smokers	p value
No.	849	65	—	826	1168	—
FVC* (liters)	4.32 \pm 0.63	4.45 \pm 0.57	NS†	3.12 \pm 0.47	3.09 \pm 0.45	NS
FEV_1 * (liters)	3.55 \pm 0.60	3.63 \pm 0.60	NS	2.56 \pm 0.46	2.53 \pm 0.44	NS
FEF_{25-75} * (liters/second)	3.91 \pm 1.24	3.77 \pm 1.13	NS	2.89 \pm 0.99	2.85 \pm 0.95	NS

* Adjusted for age, height, town presented for a mean subject (male, 42.0 years, 1.723 m; female, 42.0 years, 1.613 m).

† NS, nonsignificant; $p > 0.10$.

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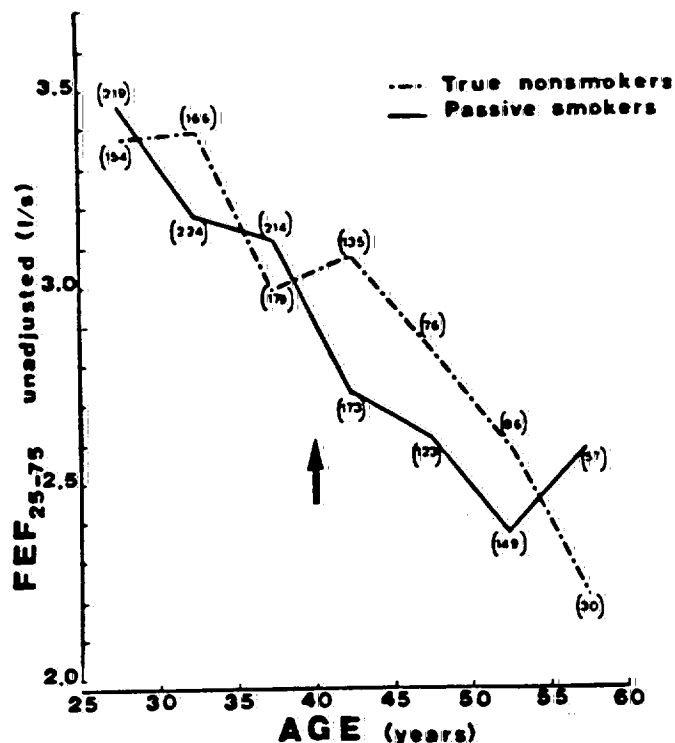


FIGURE 1. FEV₂₅₋₇₅ according to passive smoking and age among 1985 women. French Cooperative Study PAARC. Number of women shown in parentheses. Significant differences were observed for only two age groups, 30-35 years ($p = 0.04$) and 40-45 years ($p = 0.004$).

factors, in particular sociocultural data recorded in the study (social class and educational level). These variables appeared of interest because they were related both to smoking and to spirometric variables. To look at what determined the exposure to passive smoking, we investigated active smoking determinants. Active smoking was lower for men with a university degree (table 4) whereas among better educated women it increased. As expected, assortative marriage for educational level and social class was very highly significant (χ^2 4 d.f. for education level = 741). However, very highly significant resemblance in smoking habits between spouses was observed, though the association was lower than for educational level. For example, the pro-

portion of women active smokers according to their husbands' smoking habits was 10 per cent for nonsmokers, 16 per cent for ex-smokers and 24 per cent for current smokers. The high significance of this resemblance persisted after adjustment for the various sociocultural variables.

On the whole, passive smoking appeared to be related to the sociocultural variables. For instance, the educational level of the man of the house, which gives a good description of the influence of cultural habits of both members of the household, was positively associated with passive smoking among men, but negatively associated with passive smoking among women (table 4).

On the other hand, FVC, FEV₁, and FEV₂₅₋₇₅ were significantly higher in the

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TABLE 3

FVC, FEV₁, and FEF₂₅₋₇₅ (mean \pm SD) according to passive smoking among adult residents, aged 40 years or more, of seven cities throughout France, surveyed in the French Cooperative Study PAARC

	Men			Women		
	True nonsmokers	Passive smokers	p value	True nonsmokers	Passive smokers	p value
No.	423	29	—	327	501	—
FVC* (liters)	4.08 \pm 0.63	4.11 \pm 0.56	NS†	2.98 \pm 0.46	2.89 \pm 0.48	0.013
FEV ₁ *	3.31 \pm 0.58	3.19 \pm 0.60	NS	2.43 \pm 0.45	2.34 \pm 0.45	0.007
FEF ₂₅₋₇₅ * (liters/second)	3.58 \pm 1.17	3.02 \pm 0.84	0.012	2.74 \pm 0.99	2.57 \pm 0.87	0.010

* Adjusted for age, height, town, presented for a mean subject (male, 48.9 years, 1.714 m, female, 48.6 years, 1.608 m).

† NS, nonsignificant $p > 0.10$.

TABLE 4

Active and passive smoking according to the educational level of the man of the house among adult residents, aged 40 years or more, of seven cities throughout France, surveyed in the French Cooperative Study PAARC

	Educational level of the man of the house			p value
	Primary	Secondary	University	
Active smoking				
Men				
No.	1227	658	428	—
Nonsmokers (%)	25.4	23.5	25.5	
Ex-smokers (%)	19.2	22.5	27.3	0.005
Current smokers (%)	55.4	54.0	47.2	
Women				
No.	1225	652	428	—
Nonsmokers (%)	80.3	73.2	66.6	
Ex-smokers (%)	3.5	7.2	7.7	<10 ⁻³
Current smokers (%)	16.2	19.6	25.7	
Passive smoking				
Men				
No.*	253	120	79	—
Passive smokers (%)	4.4	7.5	11.4	0.07
Women				
No.*	486	223	119	—
Passive smokers (%)	63.8	59.6	48.7	0.01

* True nonsmokers + passive smokers.

upper class and the highest educational level for men and women, considering the characteristics of either husbands or wives. These differences were partly due to active smoking.

The relationships between the sociocultural variables and passive smoking on the one hand and the spirometric vari-

ables on the other decreased the association between passive smoking and FEF₂₅₋₇₅ in men. By contrast, in women, the sociocultural variables could partially explain the relationship between passive smoking and spirometric measurements. Adjusted for these variables, the differences in FEF₂₅₋₇₅ were significant for men

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adult residents,
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women	
Passive smokers	p value
501	-
39 = 0.48	0.013
14 = 0.45	0.007
7 = 0.87	0.010

1.714 m; female, 48.6

ouse among adult
yed in the

ouse	
	p value
-	-
0.005	-
-	-
<10 ⁻³	-
-	-
0.07	-
-	-
0.01	-

ceased the asso-
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and, though slightly decreased, the differences for women remained significant for FEV₁ and FEF₂₅₋₇₅. FEF₂₅₋₇₅ according to passive smoking and social class of the subjects are presented in figures 2 and 3. Note that for women the classes with reversed trend (value higher for passive smokers than for true nonsmokers) included the highest percentages of women with paid work and therefore with a true nonsmoker subgroup possibly more frequently exposed to occupational passive smoking.

The FEF₂₅₋₇₅ values of nonsmokers, passive (including light) smokers, ex-

smokers and active smokers are shown in figure 4. Among women, the light passive smokers appeared in an intermediate position between true nonsmokers and passive smokers. Women living with heavy smokers appeared to have the same values as light or moderate smokers. Among men, an unexpected pattern appeared: light passive smokers had the highest FEF₂₅₋₇₅ and passive smokers had lower values than active smokers. Though these findings could be due to the small number of men involved, the latter finding might also be explained by some selective factors, in so far as to be a male passive

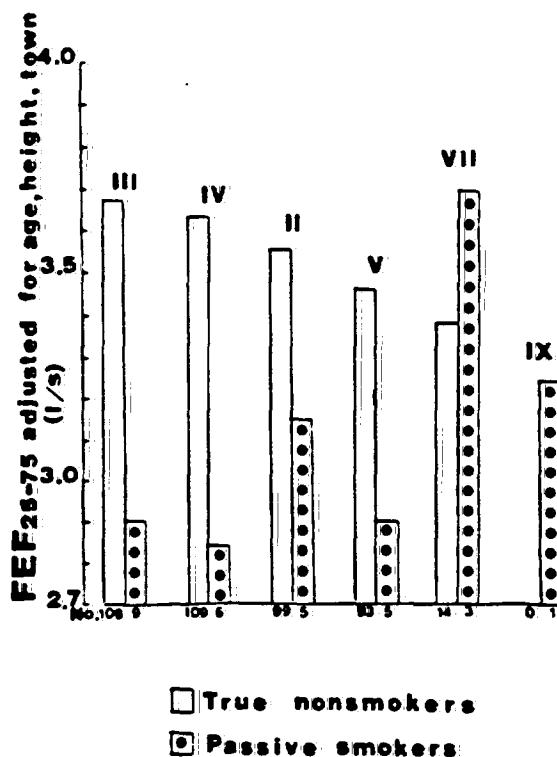


FIGURE 2. FEF₂₅₋₇₅ among men aged 40+ years according to their passive smoking and social class. French Cooperative Study PAARC. The social classes were: professional (III), intermediate (IV), self-employed (II), employees (V), personal service (VII), and never employed (IX). No significant difference was observed at the 5 per cent level in any social class considered separately. At the 10 per cent level, social classes III and IV show differences. Adjusted for social class, the difference between true nonsmokers and passive smokers was significant at the 1 per cent level.

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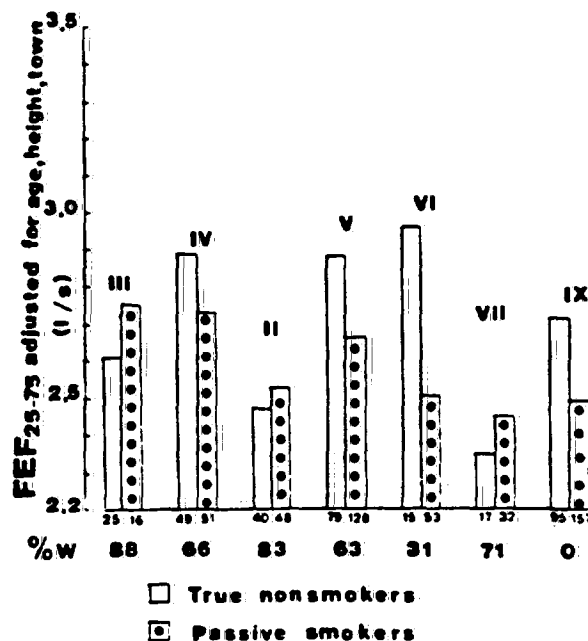


FIGURE 3. FEF_{25-75} among women aged 40+ years according to their passive smoking and social class. French Cooperative Study PAARC. "% w" represents the percentage of women with paid work at the time of the study. The social classes were: professional (III), intermediate (IV), self employed (II), employees (V), manual workers (VI), personal service (VII), and never employed (IX). No significant difference was observed at the 5 per cent level in any social class considered separately. At the 10 per cent level, social classes V, VI, and IX show differences. Adjusted for social class, the difference between true nonsmokers and passive smokers was significant at the 2 per cent level.

smoker was a rather unusual situation and this "abnormal" way of living could be related to selective factors. As a matter of fact, a higher percentage of passive smokers than true nonsmokers reported a history of asthma (17.2 vs. 7.8 per cent; $p = 0.07$) which might discourage smoking though the individuals were married to a smoker (the percentages were 4.6 for light passive smokers, 7.1 for ex-smokers, and 6.9 for active current smokers). Excluding these asthmatic subjects, the pattern observed for men was less striking but persisted, and the difference between true nonsmokers and passive smokers was of borderline significance ($p = 0.07$). Exclusion of those with a history of asthma did not modify the results among women.

Passive smoking was not related to

month of examination. Borderline significant associations were observed between female passive smoking and air pollution ($p = 0.08$) and the number of people living in the household ($p = 0.06$). However, these relationships showed no confounding trend: passive smokers made up 62 per cent in areas of low pollution, 55 per cent in areas of moderate pollution, and 65 per cent in heavily polluted areas. In households with 2, 3, 4, 5, and 6+ members, passive smoking was observed in 65, 57, 61, 46, and 63 per cent, respectively. As expected with such figures, adjustment on air pollution or number of people in the household did not change the differences observed between true nonsmokers and passive smokers.

The size of the group of female passive

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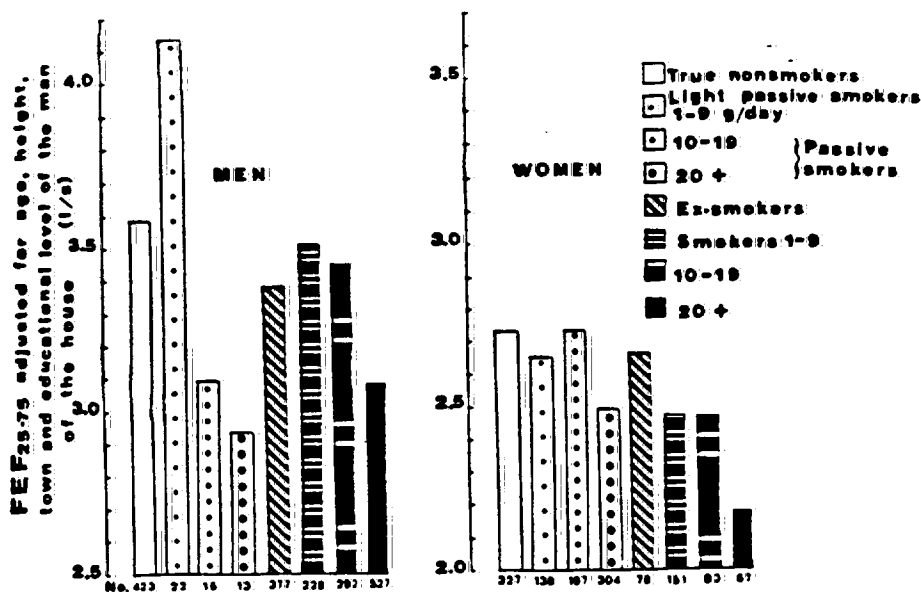


FIGURE 4. FEF_{25-75} among men and women according to active and passive smoking. French Cooperative Study PAARC. For men and women, differences in FEF_{25-75} between the eight groups were significant at the 0.001 level.

king and social class, did work at the time of d (II), employees (V), not difference was obtained level, social classes namokers and passive

borderline significance observed between and air pollution of people living (0.06). However, ved no confounders made up 62 pollution, 55 per te pollution, and olluted areas. In 5, and 6+ mems observed in 65, nt, respectively. figures, adjust-number of people change the difn true nonsmok-

f female passive

smokers allowed more detailed comparisons. In the more homogeneous group of women without paid work at the time of the study, women who were presumably less exposed to passive smoking in closed areas such as offices than the working women, a dose-effect relationship according to the amount of tobacco smoked by their husbands was evident, as shown in table 5. The difference in FEF_{25-75} remained statistically significant after adjustment for the sociocultural variables. The density of smokers/room gives another quantification of the dose. Therefore, we looked at FEF_{25-75} values according to the number of rooms. This gave the same information, however, because our passive smokers lived in households that included just one smoker. No clear conclusion arose from this approach.

DISCUSSION

The comparisons of "true" nonsmokers (persons without household exposure to

tobacco smoke) to individuals with an exposure to passive smoking consisting of living for at least 15 years with a current smoker of 10 g or more a day enable us to show a significant decrease of FEF_{25-75} with passive smoking among both men and women, which does not seem to be explained by confounding factors. A clear dose-effect relationship was shown among the women without paid work according to exposure to passive smoking. These results confirm partial data previously published on the same population (11, 12) as well as the conclusions of White and Froeb's study (2) on the noxious role of passive smoking in the work environment.

Data on gas cooking were not collected in the PAARC study. It seems nevertheless that the differences observed between true nonsmokers and passive smokers could not be due to differences in gas cooking in so far as we observed the difference for both sexes.

TABLE 5

FVC, FEV₁, and FEF₂₅₋₇₅ (mean \pm SD) according to different exposures to passive smoking among women residents, aged 40 years or more without paid work, of seven cities throughout France, surveyed in the French Cooperative Study PAARC

	Husband current smoker (g/day)				p value
	0	1-9	10-19	≥ 20	
No.	177	71	115	172	-
FVC* (liters)	2.97 \pm 0.50	2.95 \pm 0.56	2.94 \pm 0.45	2.88 \pm 0.46	NS†
FEV ₁ * (liters)	2.43 \pm 0.49	2.39 \pm 0.51	2.39 \pm 0.40	2.31 \pm 0.45	NS
FEF ₂₅₋₇₅ * (liters/second)	2.76 \pm 1.01	2.74 \pm 1.01	2.64 \pm 0.91	2.47 \pm 0.84	0.025

* Adjusted for age, height, town, presented for a mean woman 48.6 years, 1.608 m.

† NS, nonsignificant $p > 0.10$.

The two other published studies on the same topic, by Shilling et al. (3) and Comstock et al. (4), did not show significant decreases in lung function indices related to household exposure to tobacco smoke. There could be several reasons for these negative findings. The populations studied were more heterogeneous than that in the PAARC study, which excluded households "headed" by manual workers. Occupational exposure is probably a more important factor than passive smoking at home. In Shilling et al. (3), there was no assessment made of possible active smoking of other people living in the household. Their study included parents who had children who were aged only seven years, i.e., they were usually young parents. The study by Comstock et al. (4) included subjects starting at age 20 years. We found no significant difference when considering the whole PAARC population including young subjects. A certain duration of exposure was necessary to detect the effect with the indices we used. In the PAARC study, FEF₂₅₋₇₅ appeared to be a more sensitive test than FEV₁. The two other studies considered only FEV₁, or, in Comstock et al., a qualitative variable derived from it, which allowed even less powerful statistical tests than the crude values. All these factors may explain the fact that no difference was found by Shilling et al. and only a trend by Comstock et al., but the most important is probably

difference in age in so far as we found among the important group of women a significant difference in FEV₁.

Because of the very small number of studies on the effects on spirometric variables of passive smoking in the home environment, it is of interest to consider the studies on passive smoking and lung cancer. Whereas studies in Japan (13) and Greece (14) show a significant increase of lung cancer among nonsmoking women married to smokers, a study in the United States (15) did not find passive smoking to be a risk factor for lung cancer. Housing conditions are better in the US than in Japan and Greece and this can be hypothesized as an explanation for the observed results. Likewise, in France, housing conditions are not as good as in the US, particularly regarding the density of persons per room (0.5 in Comstock et al. (4) and 0.9 in the PAARC study). On theoretic and experimental grounds (16), and as demonstrated in the White and Froeb study (2) on passive smoking at work, the inefficacy of the usual conditions of ventilation to extract air polluted by smoking has been stressed. The Japanese and Greek studies were restricted to subjects aged 40 years or more, and the study by White and Froeb to subjects with 20 years' exposure. We did not find clear differences with the lung function indices we used before 40 years of age, i.e., in persons who probably had an ex-

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Passive smoking among women in France, surveyed in the

n	p value
172	-
3 = 0.46	NS ¹
1 = 0.45	NS
7 = 0.64	0.025

3 m.

so far as we found group of women a in FEV₁. y small number of spirometric varying in the home en-rest to consider the smoking and lung as in Japan (13) and nificant increase of onsmoking women study in the United passive smoking to ig cancer. Housing in the US than in and this can be eplanation for the ewise, in France, not as good as in egarding the den- n (0.5 in Comstock PAARC study). On ntal grounds (16), in the White and assive smoking at f the usual condi- o extract air pol- been stressed. The studies were re- 140 years or more, and Froeb to sub- osure. We did not ith the lung func- efore 40 years of robably had an ex-

posure of 15 years. Therefore, no conclusion can be drawn for shorter exposures.

Larger differences in FEF₂₅₋₇₅ between nonsmokers and passive smokers were observed by White and Froeb (2) than in the PAARC study. It seems that this could be related to differences in the population studied and to the type of exposure to involuntary smoking considered: the subjects they studied were selected (all working, no persistent cough, no asthma, etc.). Moreover, the occupational exposure to tobacco smoke considered was more intense than in households with one current smoker.

The comparison between the nonsmokers and the passive smokers was considered by White and Froeb as "truly experimental". This could be possible for occupational exposure; for household exposure, only women could be so described because male passive smokers were so uncommon, at least in these age groups in France, that they might be selected. The higher percentage of asthmatics among male passive smokers supports this hypothesis.

Concerning the epidemiology of smoking, our study gives data about spouses' resemblance in smoking habits. Assortative marriage for smoking habits has already been clearly shown in Scotland by Sutton (17), independently of social class and education. Because smoking habits are strongly culture-related, it is difficult to extrapolate such data to other countries. In Shilling et al. (3), 35 per cent of women and 22 per cent of men were passive smokers, while in Comstock et al. (4), 31 per cent of women and 21 per cent of men were. In our study, considering all subjects aged 25-59 years independently of the amount passively smoked as in the other studies, 47 per cent of the women and 15 per cent of the men were passive smokers (passive (including light) smokers/passive + true nonsmokers). Of women aged 40 years or more, 66 per cent were passive smokers (11 per cent for

men), but 76 per cent for Japanese women (13). Because of the large size of the female passive smoking group, as Hirayama (13) pointed out in terms of attributable risk for lung cancer, the effect of passive smoking on chronic airflow limitation might be more important in some countries than that of direct smoking among women aged 40 years or more. Our population, which showed percentages midway between the data reported in the US and Japan, could be considered as representative of the same age groups belonging to households not "headed" by a manual worker in urban areas in France. Six of the seven cities had populations of more than 300,000 and a university and the seventh had 70,000 inhabitants.

Smoking, active (because of assortative marriage for smoking) as well as passive, because of its noxious effect shown here, partly explains resemblance in spirometric measurements between spouses, which have been observed by Higgins et al. (18) as well as in the PAARC population (19).

It has been said that lung function differences between female nonsmokers and smokers is lower than among males (20, 21). Besides the observation of higher social class for female smokers and lower class for male smokers, the fact that women nonsmokers are much more often exposed to the deleterious effect of passive smoking at home could, at least partly, explain such a difference, which has not been found by other authors (22, 23). In the present study, the absolute difference in FEF₂₅₋₇₅ between true nonsmokers and smokers was higher for females than for males, even though the mean level was lower, which might better support the opposite conclusions.

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Jones, J.R., Higgins, I.T.T., Higgins, M.W., Keller, J.B. "Effects of Cooking Fuels on Lung Function in Nonsmoking Women" Archives of Environmental Health 38(4): 219-222, 1983.

ABSTRACT. A case-control study of 20- to 39-yr-old female participants in the Tecumseh Community Health Study compared use of cooking fuels and other factors in women from the highest and lowest quartiles of the lung function distribution. The forced expiratory volume in 1 second (FEV1.0) was used as the index of ventilatory lung function. The use of a kitchen exhaust fan was significantly associated with low lung function. A larger proportion of women with low FEV1.0 used gas for cooking, but this difference was not statistically significant.

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Effects of Cooking Fuels on Lung Function in Nonsmoking Women

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ABSTRACT. A case-control study of 20- to 39-yr-old female participants in the Tecumseh Community Health Study compared use of cooking fuels and other factors in women from the highest and lowest quartiles of the lung function distribution. The forced expiratory volume in 1 second ($FEV_{1.0}$) was used as the index of ventilatory lung function. The use of a kitchen exhaust fan was significantly associated with low lung function. A larger proportion of women with low $FEV_{1.0}$ used gas for cooking, but this difference was not statistically significant.

CONCENTRATIONS OF NITROGEN OXIDES (NO_x) and carbon monoxide (CO) were found to be higher in homes using gas than in homes using electricity for cooking.¹⁻³ Nitrogen oxide concentrations in gas kitchens were up to eight times those in electric kitchens.³ Indoor pollutant levels were commonly higher inside than outside the house when the oven or stove was in use. For the average person, the gas kitchen probably provides the highest exposure to these pollutants. In fact, the EPA recommended maximum 1 hr concentration⁴ for nitrogen dioxide of 500 $\mu g/m^3$ could be repeatedly exceeded in the average gas kitchen.⁵

There is evidence suggesting that persons who live in houses in which gas is used for cooking may have higher prevalence rates of respiratory symptoms, higher incidence rates of respiratory infections and

lower ventilatory lung function than persons who live in houses in which electricity is used. Melia⁶ found more cough, chest colds, and bronchitis in children from homes with gas stoves. Speizer⁷ reported a slightly lower forced expiratory volume at 1 second ($FEV_{1.0}$) and a higher rate of acute respiratory disease in children living in homes with gas cooking. Hasselblad⁸ found lower levels of FEV_{25} in 9- to 13-yr-old girls from homes with gas kitchens and Comstock⁹ noted impaired $FEV_{1.0}$ and increased frequency of respiratory symptoms in nonsmoking men exposed to gas cooking in the home. He found no evidence of similar dysfunction in women. Conversely, in a 1-yr longitudinal study, Keller¹⁰ found no significant difference in reported respiratory disease rates in persons with gas or electric kitchens.

Information collected in the Tecumseh Community

Health Study was used to test the hypothesis that nonsmoking women living in homes where gas is used for cooking have lower lung function than those living in homes where electricity is used for cooking. The Tecumseh Community Health Study is a longitudinal, epidemiologic study of chronic disease ongoing since 1959 in the population of Tecumseh, Michigan, the main purpose of which is to identify causes and precursors of cardiovascular and chronic respiratory diseases, diabetes mellitus, arthritis, and obesity."

METHODS

A sample of 213 nonsmoking women, aged 20-39 yr and consisting of all persons in the highest and lower quantiles of the FEV_{1.0} distribution, was drawn from tests conducted on the Tecumseh Community Health Study cohort in 1978 and 1979. A case control study design was used employing lung function data from the ongoing longitudinal study. Lung function values were expressed as FEV_{1.0} percent of predicted. Predicted values were based on the linear regression of FEV_{1.0} on age and height of asymptomatic nonsmoking women."

Information about factors which might affect indoor air quality and pollutant exposures was obtained by telephone interview in 1980. Questions were asked about:

- (a) primary and backup heating fuels
- (b) primary and backup cooking fuels
 - (1) time spent cooking
 - (2) use of an exhaust fan while cooking
- (c) presence of devices affecting indoor air quality (e.g., air conditioning, humidifiers, dehumidifiers)
- (d) presence of smokers in the home
- (e) age of the home

Questions were asked in 1980 but referred to exposures in 1978 and 1979. Thus the maximum recall period was 30 months. One interviewer (J.J.) did not know the subjects' level of lung function. Persons who could not be reached by phone were sent a questionnaire by mail.

The coded data were analyzed using the Michigan Interactive Data Analysis System.¹² Lung function was characterized as high or low FEV according to whether FEV_{1.0} percent of predicted was in the highest or lowest quantiles of the distribution. Responses to questions (see above and Table 1) were either categorized (heating and cooking fuels, duration of exposure to cooking fuels, kitchen exhaust fan use, presence of devices affecting air quality, presence of smokers in the home, and socioeconomic status variables) or handled as continuous data (hours spent cooking per week, age of home), depending on the particular measures. Chi-square and Student's *t* tests were used to assess associations between lung function and the response variables. Odds ratios were calculated as measures of association. Odds ratios significantly greater than 1 in-

dicate association of a factor with decreased lung function.

To examine the combined effects of various factors and their relative importance, the following multiple logistic regression model was employed:

$$\hat{p}_i = [1 + \exp(-a - \sum b_i x_i)]^{-1}$$

where \hat{p}_i is the estimated probability of disease and x_i is the value of the i^{th} risk variable. Odds ratios approximate the relative risk for each factor, conditional upon the others remaining fixed, and are calculated as e^b where e is the natural logarithm base and b_i the estimated coefficients of x_i . The model was evaluated using only the three most important contributing variables.

RESULTS

A total of 102 women with low FEVs and 103 women with high FEVs were interviewed. The response rate was 96%. Mean ages were 29.3 and 28.9 yr, respectively. The frequencies of reporting selected exposures are shown in Table 1. Only kitchen exhaust fan use was significantly associated with low lung function ($P = .04$). Of those in the lowest quantile of FEV_{1.0}, 30.4% used gas for cooking compared to 22.3% of those in the highest quantile. This difference, though in the direction suggested by the hypothesis, did not reach the 5% significance level. Long-term exposure to gas cooking (more than 10 yr) followed the same trend. There was no difference in the mean number of hours spent cooking. The use of air conditioners, humidifiers, and dehumidifiers was more frequent among those in the higher FEV quantile, but the differences were not significant. A larger proportion of women with high FEVs were exposed to smokers in the home. Socioeconomic status, as measured by the subject's education level and income, was not significantly different in the two groups.

Table 2 shows the results of the multiple logistic regression analysis. Only variables with the largest or smallest relative risks and the smallest P values were included. Use of a kitchen exhaust fan was significantly associated with low lung function ($P = .01$, Odds Ratio = 2.63). Association of low FEV and gas cooking was marginally significant ($P = .07$). Use of a dehumidifier was inversely, but not significantly related to low FEV.

DISCUSSION

The primary purpose of this study was to examine relationships of cooking fuels with lung function in women. Interpretation of the marginal association seen in the logistic model requires consideration of some methodological issues. First, electric stoves were used three times more frequently than gas stoves. A preliminary survey had suggested that gas and electric stoves were used with equal frequency. Thus, the power to detect significant differences in fuel-use between lung function categories was less than if there had been a more equal distribution of gas and electric cooking.

Table 1.—Percentage of Women with Selected Exposures by Quintile of FEV_{1,0} Percent Predicted

Characteristic	Low FEV (N = 102)	High FEV (N = 103)	Difference	Odds Ratio	P (Two-Tailed)
Gas heat	55.9	60.2	-4.3	.84	0.53
Gas cooking	30.4	22.3	8.1	1.52	0.22
Exposure to gas cooking (≥ 10 yr)	16.7	10.7	6.0	1.67	0.61
Kitchen exhaust fan use	27.4	15.5	11.9	2.06	0.04
Gas cooking and exhaust fan use	4.9	2.9	2.0	1.72	0.54
Air conditioner	36.3	42.7	-6.4	0.76	0.34
Humidifier	50.0	55.3	-5.3	0.81	0.36
Dehumidifier	23.5	29.1	-5.6	0.75	0.36
Smokers in house	32.2	39.8	-6.5	0.76	0.34
Education > high school	43.1	47.6	-4.3	0.97	0.57
Income > \$20,000/yr.	43.1	40.8	2.3	1.10	0.87

Second, the effects of gas cooking on lung function observed by other researchers were slight. Any adverse effects of gas cooking are likely to be small in comparison to the effects of other adverse determinants of lung function such as smoking and occupation. The use of nonsmoking women precludes confounding or masking of the effect of gas cooking with this factor. Harmful occupational exposures are unlikely in this group of women. Third, the population studied may not be sensitive to the exposure of interest. For example, harmful effects of gas cooking might be greater in the very young or in those with severely impaired lung function. Alternatively, the duration of exposure to cooking in this population may be insufficient to show an effect. Current fuel use may also be a poor measure of long-term exposure. Fourth, FEV_{1,0}, the usual measure of obstructive lung disease, may be insensitive to detecting any effect of gas cooking on the lung.

The association of kitchen exhaust fan use with low lung function was unexpected. A causal link seems unlikely, but fan use may be more frequent in the low FEV group because of: (1) the sensitivity of these people to ambient pollution in general and gas combustion products in particular or (2) higher levels of pollution (from undetermined sources) making fan use desirable. Use of a fan was not related to the type of cooking fuel. Exhaust fans may serve as an indicator or index variable for another probably unmeasured factor. Further definition of this factor(s) would be an area for future research.

Air conditioners, humidifiers, and dehumidifiers all tended to be more common in the homes of women with high FEVs. Whether these devices actually improve air quality from a pollutant standpoint is arguable. They may be an indirect measure of a factor such as socioeconomic status, which is directly related to level of lung function, or they may reflect a greater

concern with air quality and possibly other aspects of the physical environment.

Although some studies have shown an increased incidence of lung cancer¹³ or decreased lung function¹⁴ in nonsmokers exposed to the cigarette smoke of family members or co-workers, others have found no significant effect of nonsmoker's exposure to the smoking by family members.¹⁵ The present study showed no significant effect on FEV_{1,0} from exposure to smokers in the home. In fact, the Odds Ratio of 0.76 was less than might be expected for a potentially hazardous exposure.

No attempt was made to monitor actual indoor air pollutant burdens in the homes included in this sample and no such data were available for the community of Tecumseh. Measuring CO, NO_x, and particulates in a cross section of homes with various appliances affecting air quality would allow correlation of lung function with indoor air pollution and provide additional useful information.

A larger sample size may indicate that the use of gas stoves is related to low FEV as reported by others, but it is debatable whether the impact of these appliances on health is biologically significant. FEV_{1,0} reduction of a few milliliters in a subgroup of the population may oc-

Table 2.—Multiple Logistic Regression of Low FEV

Characteristic	Odds Ratio	P (Two-Tailed)
Gas cooking	1.82	0.076
Kitchen fan	2.63	0.010
Dehumidifier	0.64	0.116

cur in the absence of any real effect on the health of most individuals. Further research into the health effects of indoor air pollution is needed to determine whether impaired lung function is associated with the use of gas cooking or kitchen fans and, if so, to determine whether the association is causal and of any importance relative to exposure to other respiratory hazards.

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Kentner, M., Triebig, G., Weltle, D. "The Influence of Passive Smoking on Pulmonary Function-A Study of 1,351 Office Workers" Preventive Medicine 13: 656-669, 1984.

SUMMARY: Until now it has been difficult to ascertain how much passive inhalation of tobacco smoke affects bronchopulmonary function. To answer this question, an investigation involving 1,351 white collar workers was carried out. Information about active and passive tobacco smoke exposure was obtained by a standardized questionnaire. This made it possible to subdivide the overall group into five subgroups: Never smokers, passive smokers, ex-smokers, current smokers, and other smokers. Forced expiratory vital capacity (FVC) and maximal expiratory flow-volume (MEFV) curves were used for lung function analysis. From these curves FVC, forced mid-expiratory flow (FEF 25/75), forced end-expiratory flow (FEF 75/85), and maximal mid-expiratory flow (MEF 25/75) were determined and standardized for sex, age, height, and body weight. Passive smokers evaluated by this method showed essentially no decrease in parameters describing ventilatory function. It is concluded from the dose- and time-effect relationships obtained in active smokers between the lung function parameters and the duration of tobacco smoke exposure on the one hand and the daily consumption of cigarettes on the other that passive smoking in small doses may have no essential effect on pulmonary function.

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The Influence of Passive Smoking on Pulmonary Function— A Study of 1,351 Office Workers¹

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Until now it has been difficult to ascertain how much passive inhalation of tobacco smoke affects bronchopulmonary function. To answer this question, an investigation involving 1,351 white collar workers was carried out. Information about active and passive tobacco smoke exposure was obtained by a standardized questionnaire. This made it possible to subdivide the overall group into five subgroups: Never smokers, passive smokers, ex-smokers, current smokers, and other smokers. Forced expiratory vital capacity (FVC) and maximal expiratory flow-volume (MEFV) curves were used for lung function analysis. From these curves FVC, forced mid-expiratory flow (FEF 25/75), forced end-expiratory flow (FEF 75/85), and maximal mid-expiratory flow (MEF 25/75) were determined and standardized for sex, age, height, and body weight. Passive smokers evaluated by this method showed essentially no decrease in parameters describing ventilatory function. It is concluded from the dose- and time-effect relationships obtained in active smokers between the lung function parameters and the duration of tobacco smoke exposure on the one hand and the daily consumption of cigarettes on the other that passive smoking in small doses may have no essential effect on pulmonary function. © 1984 Academic Press, Inc.

INTRODUCTION

One of the numerous questions that have not yet been unequivocally answered with respect to passive smoking is its effect on bronchopulmonary function in people with healthy lungs. A number of studies in children indicate a certain negative influence, particularly in children of preschool age (11, 30, 33). Other studies, however, fail to confirm such an association (5, 18, 27, 29). Recent reviews on this subject can be found in publications by Weiss *et al.* (34) and by Lebowitz (19).

To date, only a few studies have been published on the effects of passive smoking and pulmonary function in adults (7, 14, 27, 35). These investigations were usually initiated within the framework of research projects not primarily concerned with passive smoking. As a result, certain restrictions must inevitably be made regarding the relevance of these findings. This point will be considered in more detail in the discussion. The investigation reported herein, in contrast, was designed and carried out for the sole purpose of confirming or denying any significant effects of passive smoking on the bronchopulmonary system using pulmonary function measurement.

¹ Presented at the Symposium "Medical Perspectives on Passive Smoking," April 9-12, 1984, Vienna, Austria.

² To whom reprint requests should be addressed.

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PATIENTS AND METHODS

A total of 1,351 people (941 men and 410 women) took part in the study, which was carried out in 1982-1983. Participation in the study was voluntary. All participants were white-collar workers, the majority of whom were employed in sedentary office jobs. Test subjects were recruited from the staff of an administration authority and two large industrial companies located in Northern Bavaria, a region with a relatively low level of air pollution. All those participating anonymously filled out a standardized questionnaire specially developed for this study, and upon completion handed it in a closed envelope to the person carrying out the examinations.

The pulmonary function tests were carried out with an electronic spirometer.³ The device was calibrated either daily or prior to each new series of measurements. The spirometric examination was conducted by two trained examiners with a knowledge of medicine. Special attention was paid to good cooperation on the part of the test subject with respect to the respiration exercises, which were generally repeated two to three times.

Of the various pulmonary function parameters, those listed in Table I were included in the further analysis. These parameters were identical to those used in comparable studies.

These data were transferred, anonymously, to documents designed for electronic data processing. Evaluation of the data was effected on a data processing system of the type Cyber 845.⁴ After various plausibility checks and appropriate adjustment of the data record and group, the overall group was subdivided into five subgroups (Fig. 1):

(a) *Never smokers (NS)*, defined as persons who have never been regularly exposed to tobacco smoke, either actively or passively.

(b) *Passive smokers (PS)*, defined as subjects who have never actively smoked, but who are currently exposed to passive smoking. Here, three subgroups were differentiated:

- (i) PS exclusively with household exposure to passive smoking (PS/H).
- (ii) PS exposed passively to tobacco smoke only at their place of work (PS/W), and
- (iii) persons with a combination of passive smoke exposure (PS/HW).

(c) *Ex-smokers (ES)*, defined as persons who had given up active tobacco smoking at least 6 months previously.

(d) *Current smokers (CS)*, representing the group of persons who, at the time of the investigation were actively smoking and inhaling the smoke.

(e) *Other smokers (OS)*, representing a remaining category in which noninhaling cigarette smokers and cigar and pipe smokers were grouped together.

Considerable care was expended on the standardization of the analytical pulmonary function data. For all the pulmonary function parameters, on the basis of the NS group, formulae for internal predicted values were computed, using

³ Siregnost FD10, XY Recorder E2218, Siemens, Erlangen, FRG.

⁴ Control Data Corporation, Minneapolis, Minn.

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TABLE I
THE PARAMETERS EMPLOYED FOR PULMONARY FUNCTION ANALYSIS

Method	Pulmonary function parameter	Abbreviation
Forced vital capacity curve	Forced expiratory vital capacity	FVC
	Forced mid-expiratory flow	FEF 25/75
	Forced end-expiratory flow	FEF 75/85
Maximal expiratory flow-volume curve	Maximal mid-expiratory flow	MEF 25/75

multiple regression analyses, and taking into account sex, age, height, and body weight. A comparison of the reference values thus obtained, with standard values established by other authors (4, 17, 23, 26) shows a good level of agreement. According to these figures, the standard values decrease with increasing age and weight, while an increase in height results in an elevation in the predicted value (Table 2). All the individual values actually measured were converted into a percentage deviation from the predicted standard value.

The differences in the pulmonary function parameters standardized in this way were statistically checked in a subgroup comparison, using a nonparametric test procedure. This procedure involved a comparison of several independent samples as described by Kruskal and Wallis (36). A significance level of $P \leq 0.05$ was chosen.

RESULTS

Group Structure

Table 3 shows the size, average age, and prevalence of pulmonary disease in

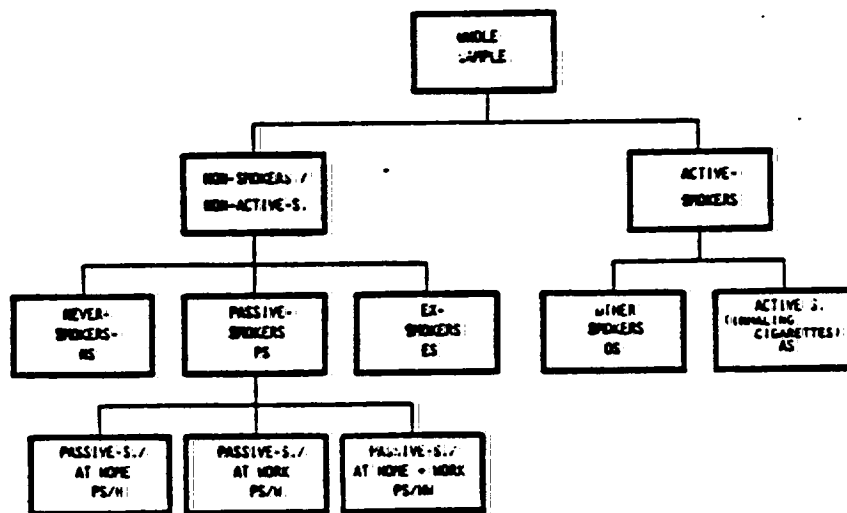


FIG. 1. Subgroups in accordance with tobacco smoke exposure criteria.

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TABLE 2
CORRECTION FACTORS FOR THE STANDARDIZATION OF THE PULMONARY FUNCTION PARAMETERS

		Age (years)	Height (m)	Weight (kg)	Const.
FVC	M	-0.028	5.71	-0.011	-3.37
(L)	F	-0.038	4.87	-0.003	-2.94
PEF 25/75	M	-0.020	4.30	-0.014	-1.72
(L/S)	F	-0.043	1.37	-0.020	1.27
PEF 75/25	M	-0.027	13.85	-0.048	-12.01
(L/S)	F	-0.091	6.48	-0.018	-0.36
MEF 25/75	M	-0.006	3.51	-0.029	-0.03
(L/S)	F	-0.023	1.84	0.031	0.03

each subgroup. The average age varies between 39 and 43 years for the men, and between 29 and 41 years for the women. Since almost all the pulmonary function parameters correlated negatively with age, the need for a standardization was thus underscored.

The CS group was most frequently affected by bronchopulmonary prior diseases, but the differences were not significant when compared with the other groups. Since on the one hand, passive inhalation of tobacco smoke may induce, or at least aggravate, chronic bronchitis, while active smoking may be the cause of this disease, the analysis of pulmonary function parameters would be affected by both including or excluding bronchitic subjects. It was, however, found that this had essentially no influence on the median values or the regression analysis. For this reason, a basic group, excluding subjects with bronchopulmonary diseases such as pneumonia, asthma, and tuberculosis in their history, but including the bronchitics, was used for further evaluation.

TABLE 3
STRUCTURE OF THE GROUP INTO SUBGROUPS, NUMBER OF SUBJECTS, AVERAGE AGE, AND BRONCHOPULMONARY PRIOR DISEASES

	No. of subjects examined		Age (median values)		Pneumonia, bronchial asthma, tuberc. of the lungs		Chronic bronchitis	
	M	F	M	F	M	F	M	F
NS	142	66	42	41	21	7	3	2
PS	251	132	40	36	30	17	8	3
ES	301	59	43	39	42	8	9	3
OS	64	12	41	29	5	2	1	2
CS	183	141	39	31	28	11	9	6
Su.	941	410	41	35	136	45	30	18

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Pulmonary Function Parameters in a Comparison of the Subgroups

In the case of FVC (Fig. 2), the median values for men are similar in all five subgroups, while, in women, only that of the CS group differs significantly from the three groups of nonsmokers.

The comparison of FEF 25/75 (Fig. 3) values shows results similar to those seen for FVC, as do the results of FEV₁, not shown here. The greatest negative deviation of the medians from the predicted FEF 25/75 values in both sexes was found in the CS group. However, no statistically significant differences were seen between the groups, which revealed a considerable scatter range for this parameter.

In Fig. 4, the FEF 75/85 values are shown. Here, ES and CS differ significantly both from NS and from PS. This, however, applies only to men.

The MEF 25/75 values show an even greater range of scatter than the prior parameters (Fig. 5). Nevertheless, here, statistically significant differentiation between the individual subgroups is possible. Thus, in the case of the men, the ES group differs from both the PS and CS, while in the women, NS and ES differ from CS.

If we compare the deviations in the predicted values of the pulmonary function parameters among the passive smoker subgroups, a heterogeneous picture is obtained. Here, FEF 25/75 (Fig. 6) and FEF 75/85 (Fig. 7) values are considered by way of example.

For the FEF 25/75 values, all the male PS groups are at about the same level (in the 100% range). By contrast, in the female PS group, a gradation is seen, with PS/W showing the smallest negative deviation from the predicted value, followed by PS/H and PS/HW (Fig. 6).

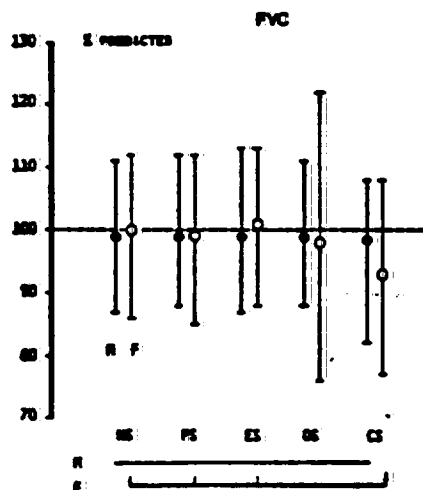


FIG. 2. Medians and 66% confidence levels of the percentage deviations from predicted values of FVC in sex-separated subgroup comparison.

FIG. 3.
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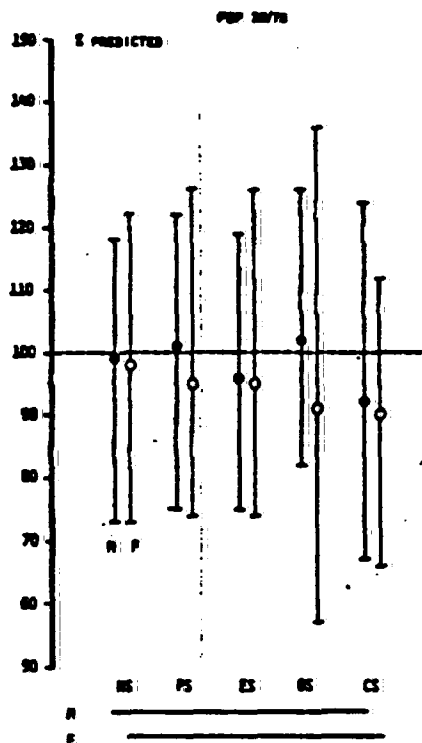


FIG. 3. Medians and 66% confidence levels of the percentage deviations from predicted values of FEF 25/75 in sex-separated subgroup comparison.

For the FEF 75/85 measurement, the situation is almost the reverse of the FEF 25/75 medians (Fig. 7). Among the men a "ranking" can be observed in that PS/H have the best function figures, followed by PS/W and PS/HW. Among the women, the medians are scattered around the 100% range in all three groups. Neither for FEF 25/75, nor for FEF 75/85, were any statistically significant group-specific differences evident.

Dose- and Time-Effect Relationships between Tobacco Smoke Exposure and Pulmonary Function

In the CS group, the individual pulmonary function parameters were correlated with both the duration of tobacco smoke exposure and the daily consumption of cigarettes. The time-effect regressions are briefly discussed for FEF 75/85.

Among men, this parameter deteriorates with increasing duration of tobacco smoke exposure. This relationship is statistically significant at the 5% level (Fig. 8). Among women, however, no statistically significant change in FEF 75/85 as a function of the duration of exposure to tobacco smoke can be seen (Fig. 9).

For parameters FVC, FEF 25/75, and MEF 25/75, dose- and time-effect re-

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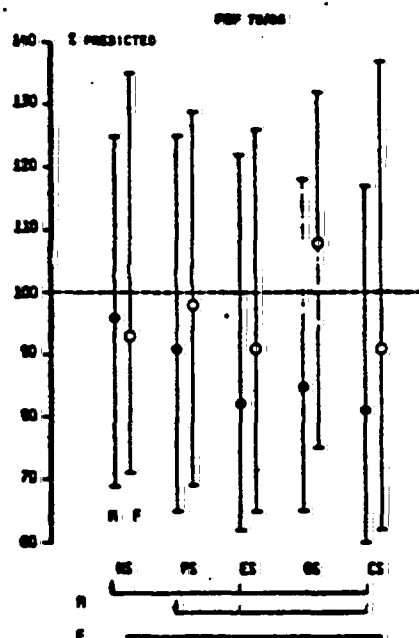


FIG. 4. Medians and 95% confidence levels of the percentage deviations from predicted values of FEF 75/85 in sex-separated subgroup comparison.

relationships with only low correlation coefficients, not statistically significant, were observed.

DISCUSSION

Inflammation of the airways is the starting point of all chronic noncarcinogenic bronchopulmonary effects of tobacco smoke inhalation (31). Although the processes which bring about functionally significant changes following the inhalation of tobacco smoke are not yet fully known, it may be assumed that they represent multifactorial processes, for which the following pathomechanisms are under discussion:

- (a) Enlargement of the mucous gland mass with resulting hypersecretion (9).
- (b) Impairment of the function of the respiratory ciliated epithelium, with build-up of secretion (3).
- (c) Increase in bronchial muscles (25), due to reflexory bronchoconstriction or direct bronchospastic effects (2).
- (d) Release of proteolytic enzymes from alveolar macrophages, with consecutive formation of a centro-acinar pulmonary emphysema after years of smoking (9).
- (e) "Displacement" of the surfactant factor (25), with possible promotion of atelectasis.

FIG. 5.
MEF 25

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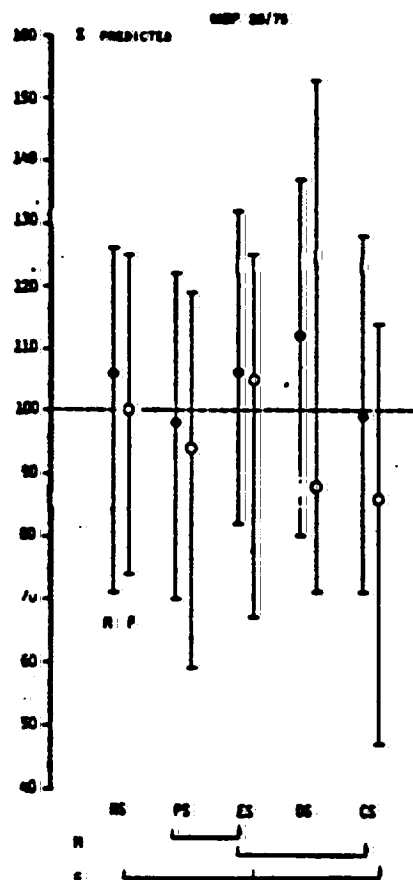


FIG. 5. Medians and 66% confidence levels of the percentage deviations from predicted values of MEF 25/75 in the sex-separated subgroup comparison.

The inflammation of the small airways represents the initial reaction of the bronchopulmonary system to the active inhalation of tobacco smoke (9, 24). This investigation is primarily concerned with clarifying the question of whether passive exposure to tobacco smoke results in function-analytical significant changes in the small airways. There is a close correlation between structural changes of the small airways and the associated effects on pulmonary function (8), although the prognostic value of these lesions with respect to severe obstructive airway diseases has not yet been established (6, 28).

The function-analytic correlate of a small airways dysfunction is, among other things, the flow limitation in the largely effort-independent, end-expiratory part of vital capacity (20, 21, 28). This results in characteristic deformations of FVC or flow volume curves, which are relatively easy to obtain in an investigation of larger groups of subjects. Although doubts have been expressed (11, 10) on the

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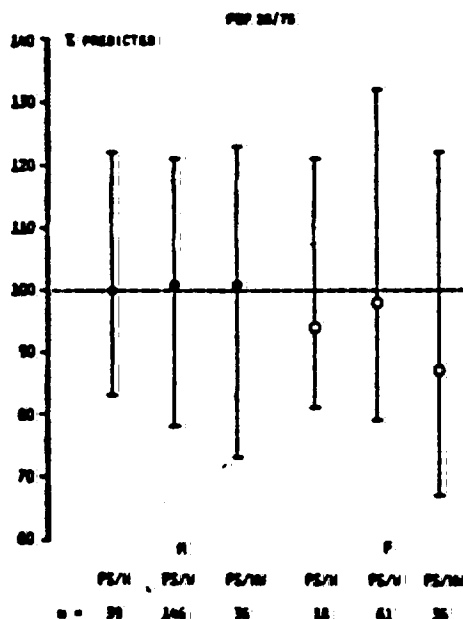


FIG. 6. Medians and 66% confidence levels of the percentage deviations from predicted values of FEF 25/75 in the sex-separated comparison, for various types of passive smoke exposure.

specificity of such pulmonary function analyses with respect to a small airways dysfunction diagnosis, the view that the determination of parameters such as FEF 25/75, FEF 75/85, and MEF 25/75, in this respect, represents a sensible and useful function-analytic method (6, 22, 28) has largely become accepted. Admittedly, the determination of flow rates or flow differences in the diagnosis of small airways dysfunction makes sense only when normal values for such spirometric parameters as FVC and FEV₁ are present (10, 22, 28), that is, when significant ventilatory and respiration-mechanical disturbances affecting the large airways can be excluded. This may be assumed, for the present study, since in all subgroups, independent of sex, the FVC values scatter only in the range of a $\pm 2\%$ deviation from the predicted norm. Only the female CS group, at -7% , represents an exception. Similar remarks also apply to the FEV₁ parameter.

It is well known that end-expiratory flow determinations are subject to a large intraindividual (6) and interindividual (16) variation spectrum. For this reason, particular care was taken in this study to eliminate as far as possible, such interfering factors as prior bronchopulmonary diseases or inhaled noxae other than tobacco smoke. Furthermore, in order to limit the danger of an evaluation bias, the study was performed under blind conditions and great importance was attached to the precise standardization of the pulmonary function measuring results.

Nevertheless, it was not possible to differentiate all five subgroups defined in accordance with tobacco smoke exposure criteria, on the basis of pulmonary function analysis. It proved possible only to discriminate the CS group from all

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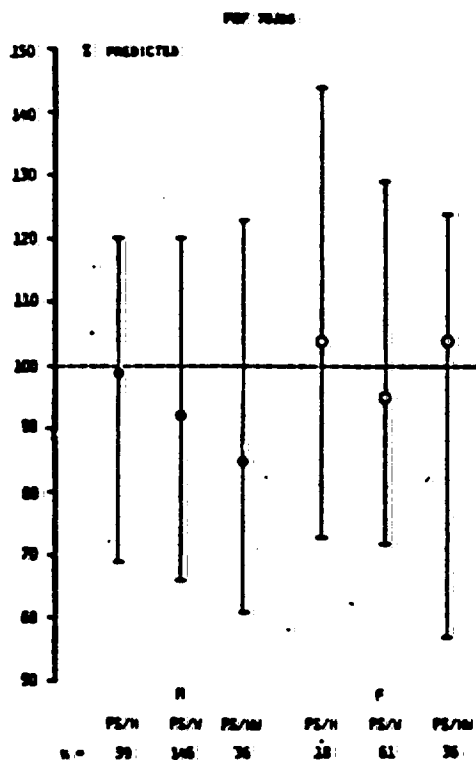


FIG. 7. Medians and 66% confidence levels of the percentage deviations from predicted values of FEF 75/85 in the sex-separated comparison, for various types of passive smoke exposure.

categories of nonsmokers and from nonactive smokers. In this connection, FEF 75/85 and MEF 25/75 revealed the greatest discrimination. Even time- and dose-effect relationships in the CS group between tobacco smoke exposure and number of cigarettes smoked per day on the one hand, and pulmonary function on the other, revealed only a few statistically significant correlations which, however, revealed inconsistencies in the sex-separated comparison. This result is possibly due to the relatively low average age of the members of the groups investigated, particularly among women.

The precision of the measuring methodology and curve evaluation may be considered good. This was demonstrated by a parallel determination of the flow volume curve for all subjects with the aid of a second electronic spirometer which determined the measured values automatically. It may, therefore, be assumed that the heterogeneity and inconsistency of the pulmonary function pattern results mainly from the large interindividual variability of the measured data. Thus, apparent correlations may also be simulated.

On the basis of the calculations of various authors (12, 13, 15, 32), for passive smokers in general, a daily exposure of the order of magnitude of 0.2 to a max-

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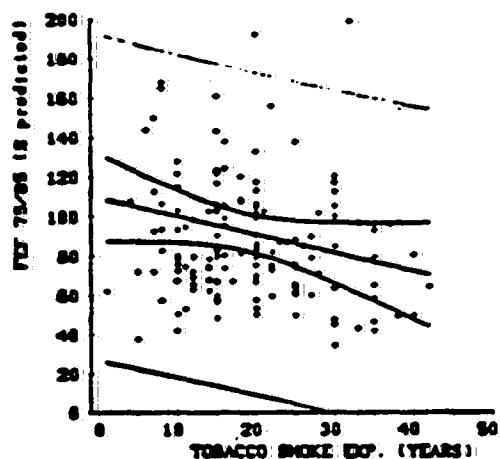


FIG. 8. Regression between FEF 75/85 and tobacco smoke exposure in years in male current smokers ($r = 0.303$, $P = 0.012$).

imum of five cigarette equivalents (depending upon the smoke constituents) may be assumed. In addition, the various types of inhalation on the part of active and passive smokers must be taken into account. While active smokers inhale primarily mainstream smoke constituents via mouth breathing, passive smokers inhale largely sidestream smoke constituents which enter the bronchial system via the nasopharynx. If additional consideration is given to the filtration function of nasal breathing, it may be stated that in the case of passive smoking one is dealing with the effects of a relatively low dose. Since, despite optimized methodology, clear and unequivocal dose- and time-effect relationships between daily cigarette consumption or smoking duration in years and pulmonary function have proved

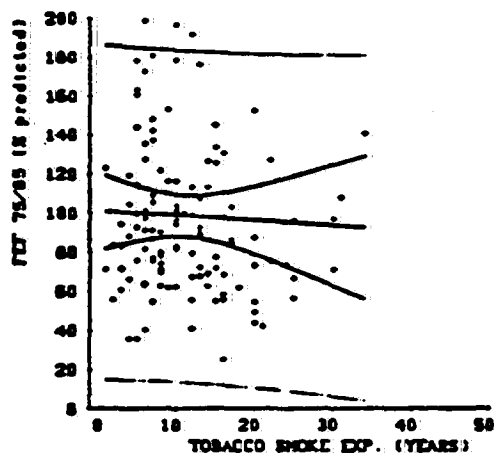


FIG. 9. Regression between FEF 75/85 and tobacco smoke exposure in years in female current smokers ($r = 0.042$, $P = 0.641$).

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impossible to establish or have been established only in an inconsistent form (as in the case of CS), this is all the more likely to be the case for the low-dose situation met with in passive smoking.

As mentioned at the beginning of this article, only a few studies have so far considered the question of possible impairment of pulmonary function in adult passive smokers. These studies all have the disadvantage, owing to the nature of the data collection, of not being able to form groups for all possible factors of active and passive tobacco smoke exposure. This means that there is a danger of selection bias involving the nonconsideration of possible positive or negative results. Since, however, a similar pulmonary function methodology was employed, comparisons between our results and those reported in other studies are possible.

In common with us, Schilling *et al.* (27) and Cumstock *et al.* (7) were unable to establish any statistically significant reduction of pulmonary function in passive smokers (Table 4). In contrast, Kauffmann *et al.* (14) found differences between

TABLE 4
REVIEW OF THE LITERATURE ON ARTICLES SO FAR PUBLISHED ON THE TOPIC PULMONARY FUNCTION
IN PASSIVE SMOKERS

Authors	Subgroups ^a	Pulmonary function parameter	Results ^a
Schilling <i>et al.</i> , 1977	NS/H N = 138 PS/H 114 CS 78	FVC, FEV ₁ PEF, MEF 50 MEF 25	No statistically significant reduction of lung function for PS/H.
White and Frueh, 1980	NS N = 400 PS/W 400 CS 1300	FVC, FEV ₁ FEF 25/75	Concerning FEF 25/75 and FEF 75/15: PS/W show statistically significantly lower values than NS. Values in PS/W do not differ essentially from values in CS smoking 1- 10 cigarettes per day and in CS without inhalation.
Cumstock	PS/H N = 539 ES/H 232 CS 953	FEV ₁ FEV ₁ /FVC	No statistically significant reduction of lung function for PS/H.
Kauffmann	NS/H N = 1675 PS/H 1223	FVC, FEV ₁ FEF 25/75	Concerning FEF 25/75 in females aged 40 years or more: statistically significant differences between NS and PS/H. Dose-effect relationship between reduction of lung function in PS/H and daily tobacco consumption of the husband.

^a See text for abbreviations.

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never smokers and passive smokers at home with regard to the FEF 25/75 parameter, and also a dose-effect relationship between the reduction in pulmonary function in passive smokers and the daily tobacco consumption of the subject's spouse. However, these relationships were statistically significant only for women, and then only for certain age groups. To date, White and Froeb (35) are the only authors who unreservedly find that passive smoking leads to an impairment of pulmonary function. The predicted value reductions in the case of persons passively exposed to tobacco smoke at the workplace do not, however, differ essentially from those seen in active smokers consuming between 1 and 10 cigarettes a day. This result is difficult to reconcile with a rational dose-effect relationship under the assumptions made earlier [see also Lebowitz (19)].

Taking our own results into consideration, it seems that the passive inhalation of tobacco smoke at home or in the workplace by healthy individuals probably does not lead to any essential impairment of pulmonary function. To what extent this also applies to extreme passive exposure to smoke must remain the subject of further investigation. Thus, for example, persons working in restaurants or in poorly ventilated rooms may be exposed to high levels of smoke pollution.

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SUMMARY: A symptom-stratified, geographic cluster sample of 117 middle class households was studied. Symptom daily diaries and peak flows were obtained for 211 subjects over a two-year period. Indoor sampling in a sample of houses was performed for O₃, TSP, RSP, CO, temperature (T), and relative humidity (RH). Questionnaires determined type of stove and number of smokers in all households. Ambient pollutants (O₃, TSP, CO, NO₂), were monitored in or near the clusters, as were T and RH. Smoking in the household was significantly correlated with TSP and RSP. Indoor CO was significantly correlated with gas stove usage. Normal young adults under age 25 had daily peak flows (PEF) associated with outdoor O₃ after adjusting for other factors). Asthmatics' PEF was associated with smoking, gas stove use and outdoor NO₂, and with outdoor O₃ and temperature, after controlling for other factors. Indoor and outdoor factors affected asthmatic symptoms, after controlling for age, sex, smoking and other ambient environmental variables.

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TECHNICAL PAPERS

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Respiratory Symptoms and Peak Flow Associated with Indoor and Outdoor Air Pollutants in the Southwest

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A symptom-stratified, geographic cluster sample of 117 middle class households was studied. Symptom daily diaries and peak flows were obtained for 211 subjects over a two-year period. Indoor sampling in a sample of houses was performed for O_3 , TSP, RSP, CO, temperature (T), and relative humidity (RH). Questionnaires determined type of stove and number of smokers in all households. Ambient pollutants (O_3 , TSP, CO, NO_2), were monitored in or near the clusters, as were T and RH . Smoking in the household was significantly correlated with TSP and RSP. Indoor CO was significantly correlated with gas stove usage. Normal young adults under age 25 had daily peak flows (PEF) associated with outdoor O_3 after adjusting for other factors). Asthmatics' PEF was associated with smoking, gas stove use and outdoor NO_2 , and with outdoor O_3 and temperature, after controlling for other factors. Indoor and outdoor factors affected asthmatic symptoms, after controlling for age, sex, smoking and other ambient environmental variables.

Recent reviews¹⁻³ have highlighted the growing importance of indoor pollutants as risks for respiratory illness. One major area of concern and controversy is involuntary cigarette smoke, especially its effects on children.^{4,5} Another area of concern has been the effects of emissions from gas stoves in the home.⁶⁻⁸ In large part, the drive for energy efficiency, to "tighten" the home environmentally, leads to much less infiltration and exfiltration, allowing pollutant concentrations to increase.¹ In addition, many new housing construction activities, such as the use of particle board and plywood, have increased levels of other gases, such as formaldehyde, such that they have the potential to produce effects on health.⁹

The accurate determination of the health effects associated with ambient pollutants, considered in part by the National Ambient Air Quality Standards, is another important consideration. As people spend most of their time indoors (75-90%), they are exposed more to indoor and less to outdoor pollutants.¹ This may indicate different exposure-response relations. Further, the nonuniformity of indoor/outdoor exposures implies different sets of indoor-outdoor exposure mixes. Thus, the relative contributions to effects on health of indoor and outdoor pollutants, and their interactions, need to be determined.

Nitrogen oxides (NO_2) and carbon monoxide (CO) are often found indoors. Studies of gas stove usage have demonstrated that levels of NO_2 are dependent on combustion efficiency and ventilation, and indoor concentrations are often higher than those outdoors.^{1,10} The impact of environmental tobacco smoke on indoor concentrations of NO_2 is usually small compared to the impact of gas stoves.¹⁰ In addition, residential wood and coal stoves are potential sources of CO and NO_2 , as well as respirable particles.¹

On the other hand, ozone occurs predominantly outdoors. Nevertheless, studies on acute effects on pulmonary function in children and adolescents¹¹⁻¹⁶ indicate a consistent finding that as outdoor ozone increases, peak flow and spirometric flow volume measures decrease in a fairly linear fashion over the range of values studied (0.01-0.15 ppm), even after controlling for temperature and other pollutants. These results are consistent with controlled human exposure studies.¹⁷ Exercise and the contribution of other pollutants and temperature appear important for the effects seen.

This paper examines daily respiratory symptoms and peak expiratory flows (PEF) in children, young adults and adults; many of the adults were chosen because they have prior respiratory conditions. It examines the influence of indoor gas use and particulate pollutants, of outdoor pollutants, and meteorological phenomena on respiratory status. This study was conducted in a representative community population sample in Tucson, Arizona.¹⁸ Previous studies in this population sample indicated the presence of relationships between weekly symptoms and both air pollutants and allergens, controlling for weather.¹⁹ Prior analyses of the present data base evaluated some effects of biological agents (algae, fungi, pollen), suspended particulate matter,²⁰ and environmental tobacco smoke.^{21,22} This paper reports on more recent findings from this study.

Methods

A total of 117 households (229 subjects) in Tucson were derived from a stratified sample of households in four geographic clusters from a representative community population under study.¹⁸ The families studied were middle class; they represented families with and without certain reported symptoms and diagnoses (asthma, allergies, airway obstruction). They were monitored over a two-year period. Daily diaries provided symptom information. Peak flows (per-

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formed between 1500 and 1900 hours each daily) were obtained using a mini-Wright peak flow meter,²³⁻²⁶ which provides results in arbitrary, relative numbers (rather than in clinical, absolute terms). The mini-Wright peak flow meters were calibrated monthly. The subjects were trained in their use by trained nurses, and monthly phone checks and seasonal visits were made to ensure proper usage. Participation of families from week to week was consistent, except for random one to two week intervals of absence (related to vacations, holidays, family crises). Individuals were absent on occasion due to incapacitating illness as well. Because family members fell into different subgroups, their absence affected the subgroup denominators differently, though randomly. There were sufficient diary responses per day (person-days; the denominator each day >5) for a majority of days in each of the seasons; the average participation per day in each symptom subgroup was 10.2-14.6 (Table I). Symptom rates per 100 person-days were calculated for each day from daily diary data within symptom groups and within exposure groups, for comparative purposes.

There were 24 in a young cohort (5-25 years) who were studied over an 11-month period in 1979-1980. After age and height correction, there was no difference between individuals in baseline peak flows (by ANOVA); all were within the normal range (within one standard deviation of 100% predicted). To remove effects of age and sex, and to avoid use of arbitrary absolute numbers, each daily PEF was converted into a standard deviation score (z -score), utilizing means and standard deviations [$z = (x_i - \bar{x})/s$] of each individual's values. Thus, values each day were deviations from individual means and all values were in the same units (with mean 0 and standard deviation 1). Average daily variations observed were compared to day to day variations in PEF in normal individuals.²³

There were 23 adult asthmatics in one of the geographic clusters, and a total of 22 other adult asthmatics, with daily peak flows. There were 321 and 354 days of observation, respectively, with sufficient information (>5 individuals/day) on these asthmatic groups. Person-days of observation for asthmatics and for other syndrome groups are shown in Table I. For adults, standard deviation scores (z -scores) of peak flows used sex-age-height specific values. Thus, all PEF were adjusted for anthropomorphic covariables, and syndrome groups retained their relative status in regard to pulmonary function (i.e., those with a syndrome like asthma, AOD have lower pulmonary function). Symptom rates were seasonal,²⁰ so season was adjusted as well, using z -scores.

Information about the characteristics of the house, yard and streets, heating, cooling, type of stove, other appliances, and smoking in the household, were obtained from all households. As reported elsewhere^{20,27,28} micro-indoor and outdoor monitoring (i.e., in and around the residence) have been conducted in a random cluster sample representative of all study households for temperature, humidity, air pollutants and aeroallergens (pollen, bacilli, fungi, and algae). Indoor total and respirable (>2.5 μ m) suspended particle (TSP and RSP) levels were related to environmental tobacco smoke but not gas stove usage, while CO levels were the reverse.²¹ Macro-monitoring for air pollutants and pollen were conducted simultaneously in the center of each of the geographic clusters, and regional air pollutant and meteorological data were provided.

Statistical analysis of daily relationships between environmental variables and respiratory responses used SPSS programs on a DEC 10-Cyber 175 computer system. Multifactorial analyses of variance (ANOVA) and regression methods were utilized to examine interactions and control for colinear variables. In the ANOVAs, regression options produced multiple analysis of covariance solutions also. Metric and nonmetric covariates were used to remove variation related to them before analyzing the independent variables. All results are presented after controlling for other

Table I. Sample size in the adult syndrome groups.

Symptom groups	No. of persons ^a	No. of person days	Mean daily denominator ^d
Asthmatics	45 ^b	6182	10.2
AOD Sx groups ^c	68	8545	14.0
Allergic subjects	62	8440	14.6
Asymptomatic subjects	29	3663	7.4

^a Only those with adequate data.

^b 23 in the asthma cluster and 22 in other clusters.

^c Airway obstructive disease symptoms.

^d More than 6 persons/day.

variables. Reported analyses usually have days as the unit of observation; some use person-days as the unit of observation. Person-days represent the denominator for each day and, thus, the sample size (Table I). When person-days were the unit of study, a person-days dummy variable was used in analysis to eliminate effects of the different number of individual person-days of observation. Unless otherwise noted, statistical significance refers to a $p < 0.05$.

Results

Indoor pollutant levels found in this study have been described previously.^{20,21,27} Briefly, indoor TSP had a maximum of 68.5 μ g/m³, while simultaneous micro-outdoor TSP reached 169.6 μ g/m³. RSP indoors reached 49.7 and outdoors 124.5 μ g/m³. The type of dust found inside, on the whole, could not be identified (using electron microscopy). Indoor CO was quite low (below 2.4 ppm) and micro-outdoor CO was below 3.8 ppm; CO correlated significantly with the presence of gas stoves. The presence of gas stoves was used as the variable qualitatively replacing NO₂ (since NO₂ measurements were not available). Neither gas stove usage nor household smoking was associated with social status (measured by education, income, occupation, crowding) in this sample. Indoor ozone (O₃) was very low indoors (measured as between 0 and 0.035 ppm). Pollen algae and fungi sampling results have been described previously.²⁰ There was no relationship between work exposures and indoor TSP or RSP; thus, no noticeable paraoccupational exposure was present.

Peak Flows in the Young

In the younger age group, more time was spent outdoors. Average daily PEF was shown to be significantly related to environmental factors (by multifactorial ANOVA, $F = 2.97$, $df = 29$ and 644, $p < 0.001$).

Further analyses were employed to examine the direct relation of O₃ to PEF. PEF was adjusted by a multiple regression for person-days, TSP, temperature and stove use ($R = 0.23$, $p < 0.001$); the other environmental factors had significant interactions with PEF. The regression of adjusted PEF on O₃ was linear with adjusted PEF = 0.287 - 6.025 O₃ ($n = 674$ person days, $p = 0.013$); the intercept and slope were both statistically significant ($p < 0.001$). Residual analysis of PEF with O₃ was significant as well (residual PEF = 0.17 - 3.20 O₃; intercept and slope statistically significant). After removing TSP (because of smaller n) and adjusting PEF for relative humidity as well, O₃ and adjusted PEF had an $R = -0.56$ ($p < 0.0001$, $n = 1513$ person days, adjusted PEF = 0.17 - 3.87 O₃); residual PEF was significantly related to O₃ as well ($p < 0.002$). Gas stove use was of borderline significance in the first regression ($p = 0.066$), but not significant ($p < 0.25$) in the second analysis.

Adults' Peak Flows

In adults, smoking had the biggest effect on PEF in every syndrome group. In normals and all allergic subjects, there were no consistent trends.

Table II. Peak flows standard deviation scores in asthmatics (asthma cluster) by outdoor ozone and temperature interaction.^a

Average maximum hourly	Maximum temperature (°F)		
O ₃ (ppm)	<61	61-80	80-96
<0.038	-1.94 (217) ^b	-1.85 (219) ^b	-2.17 (174) ^b
0.038-0.051	-1.99 (327) ^b	-1.78 (490) ^b	-1.75 (388) ^b
0.052+	-2.11 (30) ^b	-1.71 (549) ^b	-1.57 (794) ^b

^a ANOVA $F(8,312) = 9.25, p < 0.0001 (R^2 = 19.2\%)$.

^b Person-days of observation.

In 23 adult asthmatics in one geographic cluster, where indoor monitoring was most complete, PEF was significantly related to humidity indoor TSP, and active smoking. After adjusting for these other variables, PEF was significantly related to the interaction of O₃ and temperature; high temperature had an effect when O₃ was low and there was a nonsignificant trend of O₃ with PEF only in low temperature (Table II). Also, those in houses with low to moderate micro-pollen had a higher average PEF (z -score mean of -1.18) compared to those with high levels ($z = -2.51$, ANOVA, $F = 197.5, p < 0.0001$).

Asthmatics who spent 4-8 hours outdoors per day had significantly lower PEF than those with less than four hours outdoors per day ($t_3, p < 0.05$). In all asthmatics, gas stoves were associated with a significantly less average PEF (average z -score = -2.16) compared to average PEF in those with electric stoves (average z -score = -0.76, $p < 0.001$), using all person-days of observation. This held up within smoking groups as well, though the difference was greater in current smokers. (This relationship with NO₂ and gas stoves was found in allergic and normal smokers as well.) There was a significant interaction of type of stove and outdoor NO₂ with PEF. On the days when there was measurable high outdoor NO₂, it was significantly related to decreased PEF only in those with electric stoves (Table III). Those with gas stoves had significantly lower PEF than those with electric stoves when outdoor NO₂ was low.

In adults with the AOD syndrome, the overall relation of environmental variables with PEF was highly significant by multifactorial ANOVA, $F = 3.84, df = 15$ and $243, p < 0.001$. PEF was adjusted for the significant dependent effects of smoking, relative humidity, indoor TSP, and gas stove usage; the significant effect of O₃ was seen when TSP was $\leq 76 \mu\text{g}/\text{m}^3$. As there is a negative O₃-TSP correlation in this subset of days, related to their peak occurrence in different times of the year, the TSP-PEF relation was paradoxical. When these other variables were controlled in multiple regression analysis, the regression coefficient for O₃ was -5.946 ($p < 0.005$ by t test); the regression coefficient for TSP was +0.004. Since the number of days with TSP was less than half of the days with O₃ (260 vs. 586), PEF adjusted for the other variables, ignoring TSP, was related to O₃ (Table IV). The decrease in PEF on days with O₃ > 0.051 ppm is significantly different than normal day to day variation.²³

Table III. Interactive effect of gas stove usage and outdoor NO₂ on adult asthmatic average Vmax adjusted for other effects.^a

NO ₂ (ppm) ^b	Stove	
	Gas	Electric
≤ 0.264	-1.54 ^c	-1.24 ^c
0.027-0.0385	-1.53	-1.51
0.039+	-1.53	-1.65

^a ANOVA $F 15,349 = 8.7, p < 0.0001$.

^b Distribution of days divided into equal thirds.

^c t -test significant, $p < 0.01$.

Symptoms

The average daily prevalence rate for the presence of any symptom was 42.8%. Season specific prevalence rates ranged from 1.0 to 19.1% for eye irritation and 4.14-64.7% for rhinitis. The normal young cohort and asymptomatic adults ("normals") had no significant relations between symptoms and environmental factors.

"Asthma" symptoms ("attacks," wheeze, dyspnea) had significantly higher correlations with increased use of medication and increased physician visits, but their attacks were not day-of-week dependent in this study.

Temperature and precipitation had a significant interaction which was related to reported asthma symptoms in these asthmatics, as shown in Table V. (These individuals, affected also by outdoor O₃ in high temperatures, spent more time outdoors than the average.)

Table IV. Relation of adjusted daily average peak flows (standard deviation scores) with outdoor O₃ in adults with the AOD syndrome.^a

	Average maximum hourly O ₃ (ppm) ^c		
	<0.038	0.0038-0.051	0.052-0.12
Adjusted daily ^b Average PEF	-0.581	-0.582	-0.801

^a ANOVA, $p < 0.0001 (R^2 = 4.2\%), n(\text{days}) = 586$.

^b Adjusted for other significant environmental covariables.

^c Distribution divided into equal thirds.

Daily prevalence rates of productive cough in asthmatics (average of 33.2%), were corrected for age, sex, smoking, temperature, and relative humidity (all shown previously to be independently significant). The corrected rates were associated with high outdoor CO and NO₂ (occurring in winter) and gas stove usage [ANOVA, $F(15,305) = 8.96, p < 0.001$].

In allergic subjects, outdoor NO₂ was associated with increased age-sex-smoking adjusted rates of eye irritation in moderate to high temperatures [ANOVA, $F(5,493) = 24.92, p < 0.001$]. The prevalence rates progressed from 14.6% to 20% to 28.8% with increasing NO₂ (Table III).

Discussion

Subgroup division was necessary because subgroups responded differently to environmental stimuli (as shown herein). This created smaller daily denominators. Participation rates were equally distributed within and between subgroups. Further, individuals with greater daily symptomatology were not significantly over-represented in the denominators. Thus, differential participation was not a major source of bias in these analyses.

The statistical independence of daily values has been a major concern in statistical analyses of these types of data. Generally, the problem relates to the day-to-day autocorrelation in pulmonary function measures and prevalence rates. Pulmonary function is relatively stable from day to day,²³ a known biological necessity of life. Thus, one can only analyze deviations from an individual's or a group's average daily value or regression line (e.g., residuals) to reflect changes. Using multiple linear or logistic regressions does not change this phenomenon. Further, deviation values are likely to have less auto regression (unpublished data) and be distributed more closely to a Gaussian distribution.¹⁵

Incidence rates of symptoms would be independent, but the critical ones, such as asthma attacks/symptoms, occur infrequently; there were only 75 incidence days in 3820 person-days of observation. The prevalence of asthma attacks-

Table V. Prevalence rates (%) of daily "asthma attack" symptoms in asthmatics (asthma cluster).^a

Precipitation	Temperature ^b			Total	(No. of days)
	Low	Mod	High		
None or low	2.45	0.41		0.65	(276)
High	8.91	0.62		0.38	(45)
Total	3.56	0.84	0.10	0.89	(321)

^a ANOVA $F = 211.2$, $p < 0.0001$, $R^2 = 26\%$.

^b Divided into equal thirds.

/symptoms are not independent in an individual from day to day, so deviations of daily rates in a group cannot be said to be strictly independent. However, our data show that asthmatics differ greatly in their components of variance and in their contributions to variance measures over time. Thus, combining coefficients from individual multiple logistics is medically meaningless and may be incorrect statistically. The use of ANOVA for repeated measures is a promising solution to the problem; it allows one to evaluate interactions.²⁰ Using deviations from solutions of models fitted to the data decrease autocorrelations significantly and produce variates that are more normally distributed.^{15,19} The use of the two approaches together is the approach used in the analyses presented in this paper.

Those under age 25 in this study were found to spend more time outdoors and have more exercise than adults. Thus, the previous^{21,22} and present findings of an outdoor O_3 association with PEF after controlling for other variables is not surprising; it clarifies and confirms our previous studies¹⁴ and those of Lippmann *et al.*¹⁶ The interactive effects of O_3 with outdoor TSP and with temperature²¹ confirmed prior suspicions as well. However, the O_3 level at which effects were seen, though consistent, is found in a range of O_3 lower than expected (0.052–0.08 ppm) as well as in the higher range (0.08–0.12 ppm). It is conceivable that O_3 is acting as a surrogate variable. However, in the adult asthmatics, this type of analysis effectively eliminated the association of PEF and "attacks" with O_3 . The incidence rates of asthma attacks in asthmatics, based on 75 in the numerators, ranged from 2.5 to 3.8% with increasing O_3 levels, but this was not statistically significant. Surprisingly, there were no effects on symptoms noted, indicating a greater sensitivity to change of the PEF measures.^{16,22–26} The same statement can be made for normal adults in this study, whose PEF was affected by outdoor NO_2 and O_3 .

Recently, studies of the effects of gas stove usage have been performed by several groups,^{6,7} where NO_2 was measured and passive smoking was studied as well. The results have been quite contradictory in these studies and others.^{8–13,30,31} The effect of the presence of gas stoves and indoor CO (a surrogate and correlate of gas stoves) were seen in sensitive individuals. Their relations with PEF were consistent^{21,22} especially in asthmatics, and not unexpected.³ Outdoor NO_2 had such effects also. The presence of gas stoves (and/or indoor CO) was clearly related to irritant responses in adults (eye irritation, sore throat, rhinitis, peak flows).^{21,22} However, gas stove usage often interacted with outdoor pollutants or temperature in relation to many of the symptoms, and these were sometimes paradoxical.^{21,22} Thus, further studies of measured gas stove emissions, in conjunction with measures of other pollutants, are necessary.^{41,42} The interaction of active smoking, gas stove usage, and outdoor NO_2 in relation to PEF were more interesting. Unfortunately, one cannot say definitively what indoor pollutants are truly represented in this sample because of limited measurements; minor perturbations of other unmeasured pollutants may be involved also. A major interest is whether the carboxyhemoglobin and methemoglobin (from NO_2 and NO) accumulate from exposure to multiple sources (especially smoking and gas stove emissions) and act in an additive fashion as

adverse risks to health, as implied in animals.³² One could estimate that gaseous pollutants effects would be seen from environmental tobacco smoke (ETS) if its concentration were at least 3–5 times greater, the approximate degree that stove emissions exceed those of sidestream smoke,¹ or if it were nine times greater to see the same effects as active smoking, based on dose estimates of sidestream smoke.³³

Utilizing indoor measurements showed that indoor levels of total and respirable particles were high in homes with smokers.²⁷ However, there was no direct effect of ETS on children's symptoms or lung function. Indoor TSP had an effect on daily symptoms (eye irritation, productive cough) in all adults and on asthmatics' symptoms and PEF.^{21,22} However, since ETS did not,^{21,22} the relationships must be associated with other characteristics of the indoor TSP.

ETS is definitely responsible for annoyance and sensory irritant effects.^{1–3,22} However, the specific contributions of sidestream smoke to effects of personal exposures have not been sufficiently documented, and health effects in children and adults, sensitive and not, have to be clarified.²² Two studies of the effects of passive smoking on asthmatics and controls have demonstrated conflicting findings.^{34,35} We had not previously found direct effects of passive smoking in children's or adults' lung function,^{21,35} nor did we in this study. Indirectly, the relationship of O_3 with PEF seen mainly in children who were not passive smokers²² may indicate some blunting effect of passive smoking, similar to the lessened sensitivity of smokers to O_3 found in controlled human exposure studies.^{37–40}

There have been very few measurements of the extent or behavior of pollen or other microorganisms indoors. In our study, algae found outside or in evaporative coolers were not found indoors. They did not affect daily symptoms or peak flow.² Fungi were either ubiquitous or only found in one location (indoors, outdoors, or in coolers). (*Aspergillus* found indoors does not appear to produce skin test reactivity.) In preliminary analysis, they appeared to be related to symptomatology,²⁰ but the present multivariate analyses indicated they had no negative effects when other host and environmental conditions were taken into account. On the other hand, micro-pollen affected peak flow in sensitives, asthma attacks/symptoms and other symptoms in the various adult groups in this study^{21,22} and in a previous study.¹⁹ Thus, micro-pollen should be studied further as a significant environmental health phenomenon. Other aeroallergens deserve further study as well, such as cat/dog dander; pets were significantly related to asthma symptoms in our study.

In this study, sensitive groups (children, asthmatics, allergies, AOD) had more reactions to indoor and outdoor pollutants. Asthmatics appear to respond to most of the environmental factors considered. Indoor pollutants affected sensitive adults as did outdoor pollutants, and the effects of the indoor pollutant is related to the amount of time spent indoors. Unfortunately, because of sample size and the number of confounding factors, a precise exposure-effect relationship could not be determined. This would appear to be a major methodological problem for this type of study, as one must account for covariables (age, sex, smoking), symptoms (asthma, allergy, AOD), indoor and outdoor pollutant and pollen differences. Further, it is not inconceivable that O_3 or gas stoves (as examples) are acting as surrogates or indexes of some unknown factors which were not measured. Other indoor exposures were not considered in this study. Speciation of particulates may be critical as well, though not done in this study. We found that many factors related to indoor characteristics affect the strengths of the pollutants: the number of smokers in the home, the type of cooking system, fuel, the nature and volume of road surfaces, and meteorological factors. Personal exposure variables, as they indicate that subjects experience pollution levels very different from those measured at a nearby fixed monitoring station, and even different from those measured indoors,^{41,42} should be

pursued further to obtain total exposure estimates in this type of epidemiological study.

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SUMMARY: We determined air pollution exposure to sulfur dioxide (SO₂), nitrogen dioxide (NO₂) and respirable suspended particulates (RSP) for a group of symptomatic housewives and a matched control group using a specially designed domestic air pollution sampler. The NO₂ and RSP levels were higher indoors than outdoors, whereas the SO₂ levels were higher outdoors. The cases and controls showed the same air pollution exposures. The use of gas stoves resulted in elevated levels of NO₂ which might account for the observed reduction in lung function of residents in homes with gas stoves. Cigarette smoking indoors resulted in elevated particulate levels. The maximum expiratory flow (MEF) at 25% and 50% of vital capacity for non-smoking housewives showed a significant correlation with indoor particulate levels. Multiple regression analyses showed that RSP was a better predictor than NO₂ of lung function changes.

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Domestic Air Pollution and Respiratory Function in a Group of Housewives

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We determined air pollution exposure to sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and respirable suspended particulates (RSP) for a group of symptomatic housewives and a matched control group using a specially designed domestic air pollution sampler. The NO_2 and RSP levels were higher indoors than outdoors, whereas the SO_2 levels were higher outdoors. The cases and controls showed the same air pollution exposures. The use of gas stoves resulted in elevated levels of NO_2 which might account for the observed reduction in lung function of residents in homes with gas stoves. Cigarette smoking indoors resulted in elevated particulate levels. The maximum expiratory flow (MEF) at 25% and 50% of vital capacity for non-smoking housewives showed a significant correlation with indoor particulate levels. Multiple regression analyses showed that RSP was a better predictor than NO_2 of lung function changes.

A l'aide d'un appareil spécifiquement conçu pour le prélèvement de l'air domestique, on a évalué l'exposition au dioxyde de soufre (SO_2), au dioxyde d'azote (NO_2) et aux particules respirables en suspension (PRS) d'un groupe de ménagères symptomatiques et d'un groupe pairé.

Les concentrations de NO_2 et de PRS se sont avérées plus élevées à l'intérieur qu'à l'extérieur alors qu'on a observé l'inverse à l'égard des concentrations de SO_2 .

Les cas et les témoins montraient des niveaux identiques d'exposition aux polluants atmosphériques.

Dans certaines maisons, l'usage de poêles à gaz a entraîné des concentrations élevées de NO_2 ; ceci pourrait être à l'origine de la diminution des fonctions respiratoires de ces résidents.

Le fumage de cigarettes a entraîné des concentrations élevées de particules.

On a observé une corrélation significative entre les concentrations de particules à l'intérieur et le débit respiratoire maximum (DEM) à 25% et 50% de la capacité vitale des ménagères non-fumeuses.

Enclosures afford protection from outdoor pollution, but they entrap pollutants that may have seeped inside or have been generated indoors.¹ Diffusion of pollutants from outside may account for a large proportion of indoor pollution^{2,3} and may depend on passive and active ventilation.

Smoking, cleaning, and dusting generate a large amount of dust within the home.³ Lefcoe et al⁴ found that indoor levels decreased during the night, probably because of lower outdoor levels and lower indoor activity. Anderson⁵ found a high correlation between indoor and outdoor levels for SO_2 and suspended particulate. Wade et al⁶ showed that homes with gas stoves had an NO_2 source independent of outside NO_2 . Other researchers have also found gas stoves to be a

source of NO_2 in homes.⁶ Cigarette smoking indoors accounts for a large portion of suspended particulates.¹⁰⁻¹⁴

Other internal sources of pollution are aerosol sprays, heaters, humidifier systems, degrading surfaces, dried and scaling epidermis, hairs and foods.¹⁵⁻¹⁸

The evaluation of domestic factors may help to explain some of the causal factors in respiratory diseases. Reid¹⁷ found that domestic crowding was associated with coryza. Others¹⁹⁻²¹ have found crowding to be a causal factor in respiratory disease.

Colley¹⁹ showed that parental smoking had only a small effect in children's respiratory symptoms, but other studies have shown an indirect effect of smoking.²²⁻²⁴ A few studies showed no effects from passive smoking²⁵⁻²⁸ but others showed a direct effect on symptoms²⁷⁻³¹ and lung function.³²⁻³³

The use of hair spray resulted in generation of aerosols³⁴ which was not associated with lung function changes, but

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resulted in reduced mucous velocity and chest tightness. In a provocation study, test subjects showed a reduction in maximum expiratory flow,³⁷ and in an epidemiological study, aerosol spray usage was found to be correlated with respiratory symptoms.³⁸

The growth of bacteria and fungus in humidification systems may result in exposure to viable aerosols.³⁹⁻⁴¹

Keller et al.⁴² found no excess illnesses in residents who had gas stoves as compared to those with electric stoves, but children in houses with gas stoves had more bronchitis, cough and chest colds.⁴³⁻⁴⁵ Some researchers have shown an effect of using gas stoves on lung function.⁴⁶⁻⁴⁸

Binder et al.⁴⁹ found no association between exposure levels and lung function or symptoms in a group of children.

We studied exposure to three air pollutants, sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and respirable suspended particulates (RSP) in a group of housewives with respiratory symptoms; we compared the exposure with a matched group with no symptoms. Our aim was to determine whether domestic exposure was a factor in symptom causation; and to determine if a correlation existed between lung function and pollution levels.

METHODS

Exposure Measurement

Ambient air quality can be assessed with stationary sampling instruments. These characterize the air around the

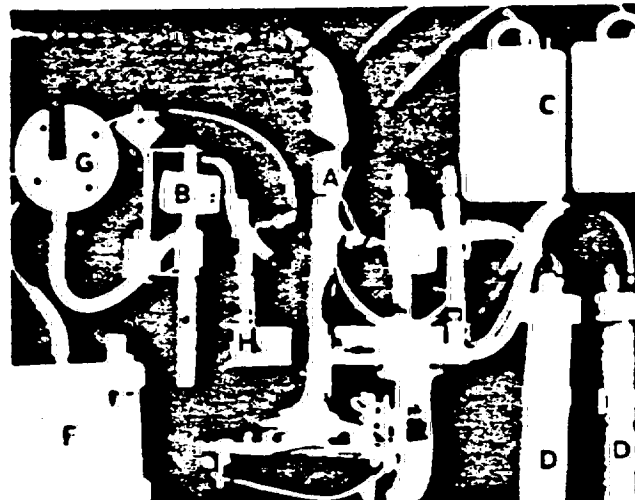


Figure 1. Multipollution Sampler for SO_2 , NO_2 and RSP

- A. Main Sampling Manifold
- B. RSP Filter with Nylon Cyclone
- C. Low Flow Pumps for SO_2 and NO_2
- D. Tubes with Absorbing Solution for SO_2 and NO_2
- E. Main Blower Pump for Mainflow
- F. Pump for RSP
- G. Dampener for RSP Pump
- H. Flow Meters

instruments but difficulties arise when the results of such measurements are used to estimate true exposure of subjects who move around, both outdoors and indoors. To obtain air quality data that might more adequately reflect an individual's changing environment, an easily portable, lightweight, and low-noise air-sampling instrument that allowed individuals to monitor their domestic environment during 24-hour periods was designed.

The instrument consisted of a manifold connected to a high volume blower which served as the main sampling source (Figure 1). Probes from the manifold led to (a) a dust sampler fitted with a cyclone assembly to collect respirable size particulates (less than $10 \mu\text{m}$) on to a fiberglass filter, (b) an impinger with a solution of potassium tetrachloromercurate to absorb sulfur dioxide, and (c) another impinger with sodium hydroxide solution to absorb nitrogen dioxide. The samplers were housed in a suitcase $50 \times 38 \times 15 \text{ cm}$ weighing 7 kg (16 lbs). The concentration for RSP was determined by gravimetric analysis, and SO_2 and NO_2 were determined by colorimetric methods.⁵⁰⁻⁵² The detection limits for RSP, SO_2 and NO_2 were $5 \mu\text{g m}^{-3}$, $3 \mu\text{g m}^{-3}$ and $10 \mu\text{g m}^{-3}$ respectively, and the recovery rates were 100%, 35% and 35%; the appropriate corrections were made for SO_2 and NO_2 recoveries.

The domestic sampling was conducted once in the summer and once in the winter. The duration of sampling each time was 24 hours.

Simultaneously, outdoor sampling for the same pollutants was conducted within a radius of 11.6 km .

Subjects were telephoned and advised that this study was a follow-up to the larger study in which they had participated earlier. A mutually agreeable time was arranged for the domestic sampling; in all cases, sampling was conducted in the homes of the cases, controls and outdoors during the same 24 hour period.

The sampler was placed in an area most used by the subject and at a height close to the breathing zone (about 1.2 m). They were advised to perform all their chores normally and to report any abnormal situations that might influence their exposure over that 24-hour period.

A short questionnaire ascertained their respiratory symptoms, smoking habits, use of heating or cooling systems, cooking methods, hobbies, housekeeping, the presence of smokers, and health conditions of others in the same house.

Subject Selection and Health Status Measurements

Housewives 25-44 years were selected for this study because they spend most of their time at home. A symptomatic group was chosen, all members responding positively to questions on "usual cough" and "usual phlegm". These subjects were matched with controls of similar age (± 5 years), who had similar smoking habits but answered negatively to the questions on "usual cough" and "usual phlegm".

These subjects were participants in a larger epidemiological study of over 7,000 people from three U.S. communi-

ties.^{20,21} The subjects were selected from two towns: Lebanon, Connecticut, and Winnsboro, South Carolina. A modified National Heart and Lung Institute questionnaire was used to determine respiratory symptoms, respiratory diseases, smoking habits, occupational exposures, domestic exposure, and sensitivities to allergens.²² Pulmonary function tests were conducted in a mobile laboratory using expiratory flow volume equipment. Five expirations were made into a pneumotachograph by each subject; the two expirations with best forced expiratory volume in one second (FEV₁) were used in computing the mean lung function.

The maximum expiratory flow volumes at 25% and 50% of vital capacity (Vmax₂₅ and Vmax₅₀) associated with these two expirations were also computed.

Calibration

The sampling equipment for SO₂ and NO₂ was calibrated against permeation tubes traceable to National Bureau of Standards. For RSP, the comparison was made against a direct reading tape sampler. This calibration was conducted in the laboratory. In all cases there were significant correlations between the sampling methods and the three comparison methods respectively ($r = 0.99$ for SO₂ and NO₂ respectively and $r = 0.88$ for RSP). SO₂ was calibrated at 5 points between 3 and 40 $\mu\text{g m}^{-3}$; NO₂ was calibrated at 7 points between 10 and 80 $\mu\text{g m}^{-3}$, and RSP was calibrated at 8 points between 20 and 80 $\mu\text{g m}^{-3}$.

The volume displacement of the maximum expiratory flow volume equipment was checked using a constant

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TABLE I
Comparison of Domestic and Outside Environments for Air Pollutants, Lebanon, Connecticut

Pollutant	Smoking Category (# of pairs)	Exposures ($\mu\text{g m}^{-3}$) ^a		Domestic	
		Season	Airway Symptoms	Control	Outside
SO ₂	non-smokers (7)	Winter	62 \pm 17	46 \pm 19	176 \pm 20
		Summer	42 \pm 22	16 \pm 68	87 \pm 15
	smokers (7)	Winter	19 \pm 76	35 \pm 78	62 \pm 18
		Summer	06 \pm 103	17 \pm 81	16 \pm 37
NO ₂	non-smokers (7)	Winter	80.9 \pm 15	74.2 \pm 16	63.9 \pm 13
		Summer	86.4 \pm 18	88.6 \pm 15	51.7 \pm 14
	smokers (7)	Winter	206 \pm 19	128.6 \pm 19	43.0 \pm 17
		Summer	103.9 \pm 14	124.1 \pm 21	16.1 \pm 17
RSP	non-smokers (7)	Winter	54.2 \pm 31	38.6 \pm 20	27.8 \pm 15
		Summer	39.6 \pm 15	31.0 \pm 16	31.5 \pm 15
	smokers (7)	Winter	101.6 \pm 17	105.3 \pm 19	22.6 \pm 16
		Summer	103.8 \pm 14	91.2 \pm 15	28.7 \pm 19

^ais geometric mean \pm geometric standard deviation.

TABLE II
Comparison of Domestic and Outside Environment for Air Pollutants, Winnsboro, South Carolina

Pollutant	Smoking Category (# of pairs)	Exposures ($\mu\text{g m}^{-3}$) ^a		Domestic	
		Season	Airway Symptoms	Control	Outside
SO ₂	non-smokers (4)	Winter	53 \pm 50	96 \pm 50	23.3 \pm 22
		Summer	13 \pm 17	0	17 \pm 28
	smokers (8)	Winter	2.8 \pm 26	4.9 \pm 35	36.6 \pm 16
		Summer	0	0	15 \pm 23
NO ₂	non-smokers (4)	Winter	70.9 \pm 1.6	75.9 \pm 1.3	17.9 \pm 11
		Summer	48.6 \pm 3.5	86.9 \pm 2.7	18.3 \pm 12
	smokers (8)	Winter	95.7 \pm 2.1	103.1 \pm 1.9	17.6 \pm 14
		Summer	87.1 \pm 1.4	82.9 \pm 1.7	21.1 \pm 13
RSP	non-smokers (4)	Winter	58.0 \pm 1.1	50.6 \pm 2.6	31.1 \pm 75.4
		Summer	33.1 \pm 3.1	25.0 \pm 31.6	75.4 \pm 13
	smokers (8)	Winter	54.1 \pm 1.6	42.3 \pm 2.7	21.8 \pm 19
		Summer	78.5 \pm 1.4	48.0 \pm 4.4	55.5 \pm 14

^ais geometric mean \pm geometric standard deviation.

TABLE III
Nitrogen Dioxide Levels in Homes with
Gas and Electric Stoves

	Gas		Electric	
	Winter	Summer	Winter	Summer
No. of observations	11	11	41	41
Geometric Mean ($\mu\text{g m}^{-3}$)	214.7	179.5	80.6	76.6
Geometric Standard Deviation	1.97	1.56	1.62	1.78
Unpaired t-test (Gas vs Electric)	$p < .001$			

volume syringe. A cam arrangement, which mimicked a typical flow volume output, was used to check the expiratory flow rates.

RESULTS

Tables I and II summarize the air pollution data for the subjects in the two towns during the winter and summer for the two smoking categories. The air pollution summary data for SO_2 , NO_2 , and RSP are given as geometric means since air pollution levels usually follow a log normal distribution.

The summary air pollution exposure data for the housewives in Lebanon and Winnsboro are shown in Tables I and II. When the data for the housewives with symptoms were compared against those without symptoms, no statistically significant differences were found. To determine whether the domestic exposure was different from the outdoor exposure the data for both housewives' groups were combined and compared against the outside air pollution data; this comparison revealed in general that the SO_2 levels were usually higher outdoors, whereas the NO_2 and RSP levels were higher indoors.

In Lebanon, the homes of smokers showed higher levels of NO_2 and RSP than the homes of non-smokers. In general the winter air pollution levels in the Lebanon homes were higher than the summer levels. In Winnsboro, the homes of smokers did not show any consistent trends, nor were there any trends between the levels in the homes during winter or summer. 21% of the homes had gas stoves, and in these NO_2 levels (Table III) were significantly higher than in homes with electric stoves ($p < .001$). This differential between homes with gas and electric stoves was seen in both seasons.

TABLE V
Effect of Gas Stove Cooking on the Lung Function of
Non-Smoking Housewives

	Mean Lung Function \pm Standard Deviation \pm			
	N	MF ₂₅	MF ₅₀	FEV ₁
Gas Stoves	3	$-32.5 \pm 25.0^{**}$	$-32.0 \pm 26.0^{**}$	$-25.3 \pm 26.2^*$
Electric Stoves	19	-1.3 ± 15.9	-2.7 ± 13.7	-2.2 ± 14.9

Unpaired t-test between gas and electric stove users. * = $P < .05$, ** = $P < .01$.
The mean values reported are the percent deviation from predicted.

The winter NO_2 levels were higher than the summer NO_2 levels in homes with both gas and electric stoves. Air-conditioned homes with gas stoves had a mean NO_2 level of $175 \mu\text{g m}^{-3}$ ($n = 4$) whereas the non-air conditioned homes with gas stoves had a mean level of $182 \mu\text{g m}^{-3}$ ($n = 7$).

5% of the homes had gas radiant heaters, but some also had gas stoves, hence it was not possible to assess the emissions of NO_2 from this source. The homes of smokers without gas stoves had a mean NO_2 level of $83 \mu\text{g m}^{-3}$ whereas homes of non-smokers without gas stoves had a mean level of $76 \mu\text{g m}^{-3}$ in the winter season; the differences were significant ($p < .001$). In the summer the means were 76 and $75 \mu\text{g m}^{-3}$ respectively.

The tests to determine the daily variations in domestic NO_2 loading showed that in two homes with gas ranges, the NO_2 levels were sometimes in excess of $1000 \mu\text{g m}^{-3}$ (i.e., 2-hourly values). In one home, 13 of the 60 2-hourly values were in excess of $1000 \mu\text{g m}^{-3}$. In this latter home, peak 2-hourly values in excess of $3000 \mu\text{g m}^{-3}$ were observed on two separate occasions. In all cases, these peaks were directly related to extensive use of the gas stoves and ovens.

Cigarette smoking contributed significantly to the RSP loading within the homes in the winter and summer (Table IV). The presence of one smoker in the home resulted in significantly more RSP than in homes with no smokers ($p < .001$), and in homes with 2 or more smokers the RSP levels were higher than homes with one smoker or no smokers ($p < .001$). In air conditioned homes with at least one smoker the mean RSP level was $81 \mu\text{g m}^{-3}$ ($n = 11$) whereas the mean RSP level in homes without air conditioning was $70 \mu\text{g m}^{-3}$ ($n = 25$).

Homes with hot water heaters with no smokers had significantly higher levels of RSP (mean $67 \mu\text{g m}^{-3}$) than homes with forced air (mean $38 \mu\text{g m}^{-3}$).

TABLE IV
Respirable Suspended Particulates as a Function of Smoking

	Number of Smokers in the Home					
	Winter			Summer		
	0	1	≥ 2	0	1	≥ 2
No. of Observations	14	18	14	14	14	14
Geometric Mean ($\mu\text{g m}^{-3}$)	40.9	47.9	75.6	35.2	56.8	84.7
Geometric Standard Deviation	2.63	2.47	2.96	1.67	1.79	1.50
Unpaired t-test	$P < .001$			$P < .001$		

TABLE VI
Lung Function of Non-Smokers Living in Homes of Smokers and Non-Smokers as a Function of Cooking Fuel Used

		Mean \pm Standard Deviation *			
Pks. day #		N	MF _{25%}	MF _{50%}	FEV ₁
Electric Stove Home					
0		36	-4.0 \pm 15.7	-0.2 \pm 12.4	-1.9 \pm 13.3
1		36	-6.7 \pm 16.5	-3.0 \pm 12.0	-0.6 \pm 15.8
2+		23	-5.9 \pm 16.0	-1.6 \pm 10.9	-1.4 \pm 23.9
Pks. day #		N	MF _{25%}	MF _{50%}	FEV ₁
Gas Stove Home					
0		6	-12.6 \pm 21.2	-8.5 \pm 25.3	-9.0 \pm 20.9
1		2	-2.2 \pm 9.1	-14.6 \pm 6.1	-9.8 \pm 11.3
2+		11	-7.0 \pm 16.8	-7.9 \pm 11.1	-6.3 \pm 14.1

* Packs of cigarettes smoked indoors.

0 = no smoker in the home

1 = 1 pk. day of cigarette smoked in the home

2 = 2 or more pk. day of cigarette smoked in the home

* See footnote, Table 5

There were no significant differences between the smoking groups for each lung function variable

To determine whether the NO₂ exposure from gas stoves resulted in impairment of lung function, non-smokers in homes with gas stoves were compared with their counterparts in homes with electric stoves (Table V). Housewives using gas stoves had significantly lower Vmax_{25%}, Vmax_{50%}, and FEV₁. However, the number of housewives in the gas stove user group was small (n = 3).

In the housewives study group, 31% of the subjects with symptoms used gas stoves, whereas 12% who used electric stoves showed symptoms. Comparing all subjects (i.e., children and adults) within these homes, 28% of the gas stove users showed symptoms whereas 18% of electric stove users showed symptoms. Both these comparisons included smokers and non-smokers.

The lung function of non-smokers who lived in homes with (a) no smokers, (b) a smoker who smoked one pack per day, and (c) a smoker who smoked two or more packs per day, were compared. In this comparison all members of the household were included and this total group was separated into those who lived in homes with electric stoves and those who lived in homes with gas stoves. In general, the lung function of non-smokers who lived in homes with electric stoves was not influenced by passive smoke (Table VI).

The lung function of non-smokers who lived in homes

with gas stoves did not appear to be affected by passive smoke, but the numbers in each smoking category was small (Table VI). The degree of correlation between the indoor air pollutants and lung function was investigated for the housewives group (non-smokers) and for all non-smoking residents in the homes of the housewives group. The analyses were conducted for NO₂ and RSP and the lung function variables of Vmax_{25%}, Vmax_{50%}, and FEV₁. SO₂ was not compared because of the extremely low indoor levels. The correlation was conducted between the log of the pollution values and the percent deviation of the lung function measures from the predicted values.

For non-smoking housewives, there were negative correlations between log NO₂ and the lung function variables, but none of these were statistically significant (Table VIII).

This group also showed negative correlations between RSP and the lung function variables, two of them being statistically significant i.e., Vmax_{25%} (p < .05) and Vmax_{50%} (p < .05) (Table VII). When all residents of the homes were studied, the effect of NO₂ on lung function was negligible, but the effect of RSP was significant for Vmax_{50%} (p < .05). For smokers there were no associations between exposure to NO₂ and RSP and lung function; an indication that the effect of smoking may override any effects of the other pollutants in the home.

There was no association between the NO₂ and RSP values.

An attempt was made to determine whether the pollutants, NO₂ and RSP, acting together would explain more of the effects on the lung function parameters. A statistical Analysis System (SAS) data set was created from the log values for NO₂ and RSP and for the percent deviation of the lung function parameters from their predicted values. A multiple regression analysis was conducted on smokers and non-smokers, for housewives, and for all residents of the homes.

The regression analysis for non-smoking housewives showed that RSP was a better predictor than NO₂ of lung function changes (Table VIII). When both NO₂ and RSP were included in the multiple regression, a larger proportion of the variation was explained, and RSP was a better predictor of Vmax_{25%} (p < .05) and Vmax_{50%} (p < .05); the effect on FEV₁ was not significant.

TABLE VII
Correlation Between Indoor Pollutants and Lung Function of Non-Smokers and Smokers

Non-Smokers	Correlation Coefficient (r)					
	MF _{25%}	Housewives only MF _{50%}	FEV ₁	MF _{25%}	All residents in the home MF _{50%}	FEV ₁
NO ₂	-.29	-.34	-.23	-.07	-.04	-.04
RSP	-.61*	-.61*	-.31	-.28	-.45*	-.39*
NO ₂	-.14	-.25	-.13	-.09	-.14	-.27
RSP	-.09	-.19	-.11	-.06	-.30	-.31

* The correlation was done on the log of the pollution concentration and the percent deviation of the lung function value from the predicted value

* p < .05

TABLE VIII
Multiple Regression of Lung Function on NO_2 and RSP of Non-Smokers and Smokers

Non-Smokers Variable	Percent of Variation			Explained by Variable (R ²)		
	Housewives Only			All Residents		
	MF_{25}	MF_{50}	FEV_1	MF_{25}	MF_{50}	FEV_1
Non-Smokers						
NO_2	8	11	5	1	11	6
RSP	1*	1*	9	8	20*	15
NO_2 & RSP	29*	34*	1*	9	20*	15
Smokers						
NO_2	2	6	2	1	2	7
RSP	8	4	1	1	9	9
NO_2 & RSP	3	11	3	1	12	15

* $P < 0.05$

† Only RSP was acting separately to explain the lung function.

TABLE IX
Daily Variation of TSP and NO_2 in the Domestic Environment

Mean 24-hour Concentration	Day 1	Day 2	Day 3	Day 4	Day 5	F-test*
TSP**	.027	.024	.015	.036	.021	1.53
NO_2 ($\mu\text{g m}^{-3}$)	38	36	30	26	44	2.59**

* F-value from one way analysis of variance. * $P > 0.05$; ** $P < 0.05$.

** TSP levels are expressed in COH Units (coefficient of haze); for this comparison a continuous particulate tape sampler was used.

When all the non-smoking residents were tested, RSP was again found to have the major effect on lung function, especially on Vmax_{50} ; the effect of NO_2 was less predominant than in the housewives group (Table VIII).

For smoking housewives, and for all smoking residents, the multiple regression analysis did not show any significant effects between lung function and the pollution values.

DISCUSSION

The domestic environment had its own generating sources for NO_2 and RSP, so much so that the levels of these two pollutants indoors were significantly higher than outdoors. Yocom et al.¹ found higher NO_2 levels in homes with gas cookers and Dockery et al.¹² found higher RSP indoors than outside. For commercial buildings, the indoor outdoor ratios were less than unity.¹⁴ The observed differences in this study may be relevant only to the rural environment since both towns had rural characteristics. It is possible that in urban environments, the indoor outdoor ratio may be less than unity.

Housewives living in homes with gas stoves had more exposure to NO_2 than those in homes with electric stoves. In some cases the concentration was observed to be as high as $3000 \mu\text{g m}^{-3}$, which potentially could cause acute respiratory reactions.¹⁴ Chronic exposure to low levels of NO_2 may result in loss of lung function and increased symptom reporting.¹⁰⁻¹² Homes with gas stoves had approximately $100 \mu\text{g m}^{-3}$ more NO_2 than homes with electric stoves.

The presence of one smoker in the home increased the RSP loading by $8 \mu\text{g m}^{-3}$ in the winter and $20 \mu\text{g m}^{-3}$ in the summer; two smokers in the home increased the levels by 35

and $50 \mu\text{g m}^{-3}$ in the winter and summer respectively.

Dockery et al.¹² found similar increases but Repace¹¹ and Weber¹³ found much higher levels. Smoking in air conditioned homes resulted in slightly higher levels of RSP compared to homes without air conditioning. Cigarette smoking indoors contributed about $2 \mu\text{g m}^{-3}$ of NO_2 in the summer and $7 \mu\text{g m}^{-3}$ in the winter.

The simple linear regression analysis between NO_2 , RSP and the lung function variables in non-smokers showed that RSP correlated well with lung function depression. The multiple regression analysis indicated that both NO_2 and RSP acted separately on the lung, but RSP was a better predictor of lung function changes than NO_2 .

The uniformity of smoking, cooking fuel use, indoor activity and type of heating system may account for the lack of differences in the mean air pollution levels between the normal and symptomatic housewives' group. Perhaps the number of subjects was too small to produce statistically significant differences in exposure levels between the cases and controls; we could not control the number of cases since only 26 met the selection criteria. The sampling schedule once in the winter and once in the summer might have been too small to define the domestic exposure because of daily variation. We tried to determine whether there was significant variation between days by sampling in a home for 5 consecutive days using direct reading instruments for suspended particulates NO_2 and SO_2 . The findings indicated (Table IX) that there was no significant variation between days for suspended particulates; the variation for NO_2 was just at the 5% significant level; and the levels of SO_2 were non-detectable. Hence the use of 2 sampling periods appear

to be adequate in defining domestic exposure for particulates and to a lesser extent NO_2 .

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SUMMARY: The relationship between lung function and environmental exposure to tobacco smoke (passive smoking) was studied in 293 nonsmoking young men and women, 15 to 35 yr of age. A self-administered mailed questionnaire was used to assess the lifetime environmental exposure to cigarette smoke at home and at work for each subject. Lung function information used here had been gathered in the course of previous study of the determinants of lung function in early adulthood. In men, maximal midexpiratory flow rate (FEF25-75) decreased in relation to an index of cumulative lifetime environmental exposure to tobacco smoke at home, after taking into account the effects of cumulative exposure at work as well as age, height, body size, respiratory pressures, and cooking fuels used at home. The components of this exposure index most closely related to the reduction in FEF25-75 were maternal smoking habits and exposure to second-hand smoke during childhood. In women, the diffusing capacity of the lung (DLco) decreased in relation to cumulative exposure to tobacco smoke at work, after accounting for the effects of cumulative lifetime exposure at home and the other factors mentioned above. These findings contribute to the gathering evidence that environmental exposure to tobacco smoke is harmful to respiratory health, and suggest that the effects are not insignificant. For instance, the FEF25-75 of a young man 20 yr of age who had never smoked and always lived at home would be 800 ml less if both his parents smoked than if they did not. Similarly, a young woman who had never smoked but had worked in an office for 10 yr where smoke was always seen or smelled would have a DLco 3 units lower than if she had worked in a smoke-free office.

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Environmental Exposure to Tobacco Smoke and Lung Function in Young Adults¹⁻³

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Introduction

The quality of indoor air (1) has emerged as one of the principal health concerns of the drive to energy conservation (2), particularly in northern latitudes where a harsh winter climate leads to strenuous efforts to diminish the dissipation of heat. A common and important source of indoor pollution is tobacco smoke, in particular, cigarette smoke (2), and Canada is among the world leaders in per capita cigarette consumption (3). Adverse effects of environmental exposure to tobacco smoke, also called passive smoking, have been demonstrated in most (4-12) but not all (13-15) studies of lung function in children. In adults, effects have been inconsistently found, but they may be more pronounced in subjects older than 40 yr of age (16-20). Adverse effects appear to be less readily demonstrable in warm dry climates (14, 15, 21). On balance, the evidence suggests dose-response relationships between exposure and any adverse effect on lung function, although estimates of exposure have been far from quantitative (22, 23). The objective of the present study was to determine whether cumulative lifetime environmental exposure to tobacco smoke in the home and/or at work affects the lung function of young adults 15 to 35 yr of age. This age group has not previously been the target of investigation, and such cross-sectional data as exist do not point to adverse lung function effects (16, 18). This is somewhat surprising since a recent longitudinal study suggests that passive exposure to maternal cigarette smoke reduced the rate of lung function growth of young persons 4 to 28 yr of age (7). In the present research, an effort was made to develop a cumulative index of lifetime exposure of a more quantitative nature than the essentially qualitative indices used previously.

Methods

The study combined data from two sources: (1) lung function information collected in 1980-1981 as part of a cross-sectional study

SUMMARY The relationship between lung function and environmental exposure to tobacco smoke (passive smoking) was studied in 293 nonsmoking young men and women, 15 to 35 yr of age. A self-administered mailed questionnaire was used to assess the lifetime environmental exposure to cigarette smoke at home and at work for each subject. Lung function information used here had been gathered in the course of a previous study of the determinants of lung function in early adulthood. In men, maximal midexpiratory flow rate (FEF₂₅₋₇₅) decreased in relation to an index of cumulative lifetime environmental exposure to tobacco smoke at home, after taking into account the effects of cumulative exposure at work as well as age, height, body size, respiratory pressures, and cooking fuels used at home. The components of this exposure index most closely related to the reduction in FEF₂₅₋₇₅ were maternal smoking habits and exposure to second-hand smoke during childhood. In women, the diffusing capacity of the lung (DLCO) decreased in relation to cumulative exposure to tobacco smoke at work, after accounting for the effects of cumulative lifetime exposure at home and the other factors mentioned above. These findings contribute to the gathering evidence that environmental exposure to tobacco smoke is harmful to respiratory health, and suggest that the effects are not insignificant. For instance, the FEF₂₅₋₇₅ of a young man 20 yr of age who had never smoked and always lived at home would be 800 ml less if both his parents smoked than if they did not. Similarly, a young woman who had never smoked but had worked in an office for 10 yr where smoke was always seen or smelled would have a DLCO 3 units lower than if she had worked in a smoke-free office.

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investigating the evolution of lung function in the transition from adolescence to early adulthood in approximately 900 young adults without occupational exposure to dust or fumes (24) (hereafter referred to as the parent study), and (2) information on their lifetime environmental exposure to tobacco smoke and other home pollutants obtained by means of a questionnaire developed specifically for the purposes of the present study. The questionnaire was mailed during 1983 and 1984 to all participants of the parent study. Only subjects who reported never having smoked regularly before the date of the lung function tests were retained for analysis.

Study Population and Lung Function Data

The parent study has been reported in full elsewhere (24). In brief, subjects in the target age group (15 to 35 yr of age) were recruited on a volunteer basis from a school, a junior college, and two downtown Montreal banking institutions (table 1). They answered an interviewer-administered respiratory symptom questionnaire (ATS-DLD) (25) that included questions on smoking, and they performed the following lung function tests: (1) forced expiratory flow-volume curves with measurements of FVC, FEV₁, peak expiratory flow rate (PEFR), forced expiratory flow rate in the middle half of the FVC (FEF₂₅₋₇₅), and forced expiratory flow rates after 50 and 75% of FVC had been expelled (Vmax₅₀ and Vmax₇₅); (2) single-breath diffusing capacity for carbon monoxide (DLCO) with correction for back pressure calculated from carboxyhemoglobin (COHb%) measured by an oxygen rebreathing technique; (3) FRC measured by a constant pressure volume displacement plethysmograph. The slow VC was also recorded to allow calculation of residual volume (RV) and TLC. Further details on techniques, calculations, procedure, and selection of measurements used to characterize each participant's lung function are given in the earlier report (24).

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TABLE 1
SOURCE OF THE STUDY POPULATION

Institution	Target*	Contacted†	Responded‡	
			(n)	(%)§
Bank 1	420	372	303	81.4
Bank 2	229	225	183	72.4
College	120	109	84	77.1
High school	128	112	86	78.8
Total	897	818	636	77.8

* Studied in a cross-sectional respiratory survey carried out in 1980/1981 (24).

† Through the institution or a home address recorded at the time of the previous survey.

‡ Percentage of those contacted.

Environmental Exposures at Home and at Work

The questionnaire used to assess environmental exposures was divided into two parts: home exposures and work exposures. A separate section dealt with home exposures to cooking and heating fuels. An introductory letter asking the subjects to participate in a study on indoor air quality and lung function accompanied the questionnaire. To assist the subject's recall of past exposures, separate subsections of the questionnaire made up of the same series of questions dealt with the following seven life reference periods: 5 yr of age and less (preschool), 6 to 11 yr of age (elementary school), 12 to 17 yr of age (high school), 18 to 22 yr of age (college for some), and 23 to 27, 28 to 32, and older than 32 yr of age. For each time period, the subject was asked how many persons lived in the same house and how many smoked; if there were smokers, the relationship to the subject was ascertained, and the average daily cigarette use was established based on the following code: light, less than 10 cigarettes; moderate, less than 20; heavy, 20 or more. In addition, use of cigars or pipes by household members was ascertained.

In the case of bank employees, the exposure to environmental tobacco smoke at work was assessed. Subjects were asked to report on the habitual "smoke conditions" that were present in each "area" in which they had ever been employed, both at the bank and earlier in their career. If tobacco smoke was seen and/or smelled occasionally, the exposure was considered light; if such was usually the case, the exposure was labeled moderate; and if that was always so, the work exposure was considered heavy. In the case of the students, it was assumed that they were not exposed during classes. The final two sections of the questionnaire dealt with the personal smoking habits of the subject and certain respiratory symptoms (copies of the questionnaire are available on request).

Indices of Environmental Exposure to Tobacco Smoke at Home

The questionnaire yielded two indices of cumulative exposure. The first was obtained from the product of the number of house-

TABLE 2
CHARACTERISTICS OF THE 293 NONSMOKING SUBJECTS* IN WHOM THE EFFECTS OF ENVIRONMENTAL EXPOSURE TO TOBACCO SMOKE WERE STUDIED

	Men (n = 133)			Women (n = 160)		
	Mean	SD	Range	Mean	SD	Range
Age, yr	24.8	6.7	14-36	22.6	6.2	13-35
Height, cm	176.7	6.5	158-190	162.6	5.8	145-178
Weight, kg	72.8	11.0	52-108	58.6	8.0	36-90
COHb, %†	1.89	1.24	0-4.88	1.81	1.46	0-8.12
Cumulative exposure to smoke in the home (persons × years)	21.2	17.0	0-84.0	22.8	17.4	0-75.0
Cumulative exposure to smoke at work (packs/day × years)	1.9	3.0	0-17.1	2.0	3.6	0-23.8

* Answered no to the following questions: Have you ever smoked cigarettes? (No means less than 20 packs of cigarettes or 12 oz. of tobacco in a lifetime, or less than 1 cigarette a day for 1 yr.) Have you ever smoked a pipe regularly? Have you ever smoked cigars regularly? (Questions 25A, 26A, and 27A of the ATS-DLD questionnaire (25).)

† Five women had values greater than 5 g/L; these high values may have been due to incorrect reporting (the subjects were nonsmokers), technical error of measurement, or heavy environmental exposure.

hold members who smoked and the number of years living in the same household as the subject (persons × years). The second index was obtained by summing the product of the number of packs smoked per day by each smoker in the household and the years he/she lived in the same home as the subject (packs per day × persons × years). Packs per day were calculated from the code used by the subject in the questionnaire to describe the family members' smoking habits as follows: light, moderate, and heavy smoking habits were assigned values of 5, 15, and 25 cigarettes per day, respectively; if unknown, i.e., if a family member smoked but it was not known how many cigarettes, a value of 7 cigarettes per day was assigned, and the total was converted to packs per day assuming 1 pack equals 20 cigarettes.

Indices of Exposure to Tobacco Smoke at Work

Bank employees were asked to assess smoke conditions in the work area as light, moderate, heavy, or unable to quantify. These qualitative assessments were arbitrarily converted to number of cigarettes as follows: light = 5, moderate = 15, heavy = 25, unable to quantify = 7. The total was divided by 20 to yield packs and multiplied by duration to yield pack-years of exposure at work. For calculations of both home and work exposure indices, exposure that occurred after the date of the lung function test was excluded.

Indices of Exposure to Home Cooking Fuels

The length of time living in homes using natural gas or electricity as a cooking fuel was calculated for each subject, yielding two indices of exposure to cooking fuel expressed in years of exposure.

Analysis

The contribution of the indices of environmental exposure to the prediction of lung function test results was examined using multiple linear regression (SAS statistical package, GLM procedure) (26). Men and women

were analyzed separately. Each regression model contained age, height, Quetelet index ($100 \times \text{weight}/\text{height}^2$), respiratory pressures, and cumulative exposure to cooking fuels at home. When examining the effect of exposure at home, cumulative exposure at work was included in the regression equation. When examining for the effect of exposure at work, cumulative exposure at home (persons × years) was included in the predictive model.

Results

Two hundred ninety-three subjects in the parent study (133 men, 160 women) were considered to be nonsmokers according to their answers to the questionnaire administered at the time of the lung function tests. Other descriptive characteristics are shown in table 2, and the definition of a nonsmoker is made explicit in the footnote to this table; table 3 provides the mean lung function results for these subjects.

The principal study results are presented in table 4. Exposure at home (expressed as persons × years), and at work (expressed as packs/day × years) was similar in men and women. However, inverse relationships between lung functions and environmental exposure were found more often in men than in women.

For instance, in men there were inverse relationships between cumulative exposure to environmental tobacco smoke in the home (persons × years) and flows at low lung volumes ($\text{FEF}_{0.75}$, $p < 0.01$; \dot{V}_{max} , $p < 0.05$ and less strong for \dot{V}_{max} , $p = 0.06$). Similar relationships were found when the cumulative exposure at home was expressed as packs/day × persons × years (data not shown). However, the greater variability in this latter measure of exposure with larger standard errors reduced the level of statistical significance. When parti-

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TABLE 3
LUNG FUNCTIONS IN 293 NONSMOKING SUBJECTS

Lung Function	Men (n = 133)*		Women (n = 160)*	
	Mean	SD	Mean	SD
Derivatives of the flow-volume curves				
FVC, L	5.18	0.73	3.80	0.55
FEV ₁ , L	4.49	0.63	3.23	0.48
PEFR, L/s	10.6	2.72	7.2	2.48
FEF ₂₅₋₇₅ , L/s	5.29	1.44	4.19	1.07
Vmax ₂₅ , L/s	8.36	1.86	6.01	1.18
Vmax ₇₅ , L/s	3.26	1.12	2.65	0.85
Lung volumes				
VC, L	5.42	0.78	3.72	0.64
RV, L	2.04	0.73	1.68	0.62
TLC, L	7.27	1.13	5.29	0.89
Diffusing capacity for CO (single breath), ml/min/mm				
	34.3	6.1	23.3	4.5

* Not all subjects completed all tests satisfactorily; the lowest numbers were for lung volumes (124 men, 148 women). FVC and FEV₁ were completed by all.

tioning the home exposure according to the family member who smoked, an inverse relationship between the FEF₂₅₋₇₅ and maternal smoking habits was also demonstrated with a regression coefficient for FEF₂₅₋₇₅ of 0.04 L/s per pack/day per year that the mother smoked ($p < 0.05$). The effect of environmental tobacco smoke exposure in the different periods of life was also examined. In men, but not in women, a statistically significant inverse association between exposure before 17 yr of age and FEF₂₅₋₇₅ was found. When the analyses were restricted to the exposure during the 5 yr immediately preceding the lung function tests, no such association was observed. A small decrease in RV with increasing cumulative exposure at home (persons \times years) was also found in men. The cumulative exposure to environmental tobacco smoke at work was much lower than that at home. There was, however, an inverse relationship between the slow VC and increasing exposure at work in men ($p < 0.05$).

In women, there was no significant relationship between any of the lung functions measured and cumulative exposure to environmental tobacco smoke at home (persons \times years or packs/day \times years). However, cumulative exposure at work (packs/day \times years) showed a statistically significant inverse relationship to DLCO, but had no effect on spirometric parameters or lung volumes.

Discussion

The present results suggest that environmental exposure to tobacco smoke during the growth period of the lungs, especially early in life, permanently affects

their mechanical properties in young men (reflected in changes in derivatives of the flow-volume curve), whereas exposure to second-hand smoke at work affects the diffusing characteristics of the lung in young women. These findings complement published data implicating home exposure, particularly to mothers' cigarette smoking. Thus, inverse relationships between environmental exposure to tobacco smoke and parameters derived from the FVC maneuver (27) have been described in both sexes, though the relative effects in males and females vary in different studies, and there are also inconsistencies between studies as to relative deficits in large or small airways function (23). Our findings demonstrating

mostly small airways abnormality in men are consistent with those of Taussig and coworkers (28, 29), who have reported differences in the mechanical properties of the lung with greater susceptibility to small airways obstruction in boys than in girls. Male-female differences similar to our own results have also been reported in young active smokers (30).

The effect of environmental exposure to tobacco smoke at work on the diffusing capacity of young women has not to our knowledge been previously documented. This is due at least in part to the lack of studies examining the long-term consequences of this exposure in the workplace (31). In a similar age group, Enjeti and coworkers (30) found decreases in diffusing capacity in relation to active smoking more prominent in females than in males. These sex differences may reflect distinct pathophysiologic responses to environmental agents, which may in turn contribute to the sex differences in the incidence of chronic airflow obstruction and primary pulmonary hypertension.

Mild reductions in some lung volumes (RV) in relation to exposure at home and at work (VC, TLC) were found in men only. These reductions in lung volumes may represent a decrement in lung growth analogous to that reported in children for FEV₁ in relation to environmental exposure to tobacco smoke (7). However, caution in interpretation is needed since the multiple tests of significance (involving both exposure and response measure-

TABLE 4
REGRESSION COEFFICIENTS OF LUNG FUNCTIONS ON INDICES OF CUMULATIVE EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE*

Exposure Index (units)	Men		Women	
	Home (persons \times years)	Work (packs/day \times years)	Home (persons \times years)	Work (packs/day \times years)
Mean (maximum)	21.2 (84.0)	1.9 (17.1)	22.8 (75.0)	2.0 (23.8)
Flow-volume curves				
FVC	0.001	-0.038	0.022	-0.009
FEV ₁	-0.002	-0.022	-0.001	-0.011
PEFR	-0.010	-0.018	0.003	-0.025
FEF ₂₅₋₇₅	-0.020 [§]	0.024	-0.003	-0.023
Vmax ₂₅	-0.020 [§]	0.015	0.003	-0.014
Vmax ₇₅	-0.012 [†]	0.012	-0.001	-0.007
Lung volumes				
VC	0.004	-0.045 [‡]	0.001	-0.006
RV	-0.008 [‡]	-0.023	-0.000	0.006
TLC	-0.003	-0.089 [†]	-0.001	0.002
Diffusing Capacity	0.020	-0.202	-0.007	-0.258 [‡]

* All regression coefficients are adjusted for age, height, Quetelet index, respiratory pressures, and cumulative exposure to cooking fuels at home. Coefficients for exposure at home are adjusted for cumulative exposure at work; coefficients for exposure at work are adjusted for cumulative exposure at home.

[†] $p < 0.10$

[‡] $p < 0.05$

[§] $p < 0.01$

ments) are likely to have resulted in some associations achieving statistical significance by chance. On the other hand, some of the associations suggest effects that are by no means insignificant. For instance, the FEF₂₅₋₇₅ of a young man 20 yr of age who had never smoked and always been at home would be 800 ml less if both his parents smoked than if they did not. Similarly, a young woman who had never smoked but who had worked in an office for 10 yr where smoke was always seen or smelled would have a DLCO 3 units lower than if she had worked in a smoke-free office.

In most previous studies containing subjects in a similar age group, no relation between lung function and environmental tobacco exposure was found (16, 18, 19). Reasons for positive findings in this study may include our use of a cumulative and essentially quantitative estimate of exposure rather than a qualitative one (22, 23) with, in consequence, a lessening of the attenuation of dose-response relationships that inevitably accompanies misclassification (32). The use of a questionnaire to assess a subject's exposure to second-hand smoke has been validated, at least for recent exposure (33). However, the assessment of past exposure by questionnaire has limitations (34) that are likely to have caused an underestimation of the actual lung function deficit attributable to second-hand smoke.

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This investigation was undertaken in 1982 to explore the association between passive smoking and chronic obstructive pulmonary disease in adults in Greece. The subjects were 103 non-smoking ever-married women residents of the Greater Athens area and their 179 matched controls. Exposure was evaluated based on the smoking habits of the husband. The authors reportedly found a statistically significant ($p < 0.05$) linear trend between amount of tobacco smoked by the husband and risk of hospitalization for COPD. The authors estimated an adjusted relative risk of 1.3 for women whose husbands smoked less than 300,000 cigarettes (life-long total) and of 1.8 for women whose husbands smoked more than 300,000 cigarettes (life-long total). The authors conclude that "it appears that exposure to environmental tobacco smoke may contribute to the development of COPD with an associated relative risk of about 2."

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The Effect of Involuntary Smoking on the Occurrence of Chronic Obstructive Pulmonary Disease

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Mainstream smoke (MS) is the tobacco smoke that is drawn through the butt end into the smoker's respiratory system. Sidestream smoke (SS) comes directly from the burning end of the cigarette. «Passive smoking», «involuntary smoking» and exposure to «environmental tobacco smoke» (ETS) are used synonymously in the literature to describe the exposure of non-smokers to elements of tobacco smoke generated by smokers [1, 2]. Despite qualitative differences between mainstream smoke and sidestream smoke, it has been customary to assume that exposures to ETS approximate a low-dose exposure to tobacco smoke. Since cigarette smoking is the major cause of Chronic Obstructive Pulmonary Disease (COPD), morbidity and mortality in most countries of the world, and children of smoking parents have (i) increased prevalence of reported respiratory symptoms, (ii) increased frequency of bronchitis and pneumonia early in life, and (iii) measurable though small differences in tests of pulmonary function, when compared with children of non-smoking parents [3], an effect of passive smoking in adults should not be excluded. Having undertaken in the late 70's a study to explore the association between involuntary smoking and lung cancer [4], it was decided in 1982 to undertake a similar study to investigate the association between involuntary smoking and COPD in adults in Greece. The study was restricted to non-smoking ever-married women residents of the Greater Athens area. Among relatively older Greeks the prevalence of smoking is very high in men but relatively rare in women, making a passive smoking study in women, rather than in men, considerably more efficient. As in most of the studies concerning involuntary smoking and lung cancer, the present study evaluated exposure to passive smoking on the basis of the smoking habits of the husband. The underlying assumptions in this approach are (i) that a smoking husband is the main source of passive smoking for a relatively older woman; (ii) that information concerning the smoking behaviour of a husband is much more reliable than information concerning other sources of passive smoking; (iii) that non-smokers married to smokers are likely to be more tolerant towards other sources of passive smoking; and (iv) that smokers tend to cluster.

This investigation was part of the Professorial Thesis of one of us (ST) and University rules did not allow the publication of the results before the thesis was submitted to the Medical School at the fall of 1987.

Material and Method

Between January 1982 and December 1983, 137 ever-married women 40-79 years old were admitted to the Seventh Clinic of the Teaching Hospital for Respiratory Diseases in Athens with a diagnosis of COPD. Single women were not included in the study since their life-styles in Greece are sufficiently different from those of married women. Women younger than 40 and older than 80 were not included in the study because very young women could not have been exposed to their husband's smoking for a period long enough to accommodate the postulated latency of COPD, whereas information coming from very old women could be less reliable than information provided from younger women. Women were included in the study if they were hospitalized for the first time with principal diagnosis of COPD. The case series included patients who were presented with dyspnoea on exertion and expectoration for at least 3 years, and who were found in the laboratory to have obstructive or mixed type reduction of pulmonary function by at least 20% in forced expiratory volume in 1s, without improvement after bronchodilatation [3]. Seven women with a history of bronchial asthma or familiar history of pulmonary emphysema were excluded from the study whereas two additional women refused to be interviewed. Among the remaining 128 women of the index series 18 were current and 7 have been past smokers and were excluded from further analysis. (Smoking status was ascertained with reference point one year before the interview; thus those who stopped smoking six months before the interview were counted as current smokers). The remaining 103 women have twice denied that they have ever been smokers, once during their routine history-taking and then categorically at interview in the study. Controls were 206 ever-married women of similar age who were visitors (friends or relatives) of patients at the hospital during the same period. Six women refused to be interviewed and among the remaining 200, 7 were current and 14

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have been past smokers and were excluded from further analysis. Thus, the analysis was based on 103 cases and 179 controls—all ever married women who have never been smokers.

Following earlier Greek experience as well as international practice [4-7] the smoking habits of the husband were taken as indicators of exposure to environmental tobacco smoke. More specifically, exposure variables were based on husband's smoking habits in terms of amount (non-smoker, ex-smoker of any specified amount, and current smoker by average daily number of cigarettes; smoking of other forms of tobacco is rare in Greece), duration (beginning from the date of marriage or start of smoking by the husband, whichever came later, and ending at the date that the husband died or stopped smoking or current date, whichever came first), or their product (total number of cigarettes smoked).

In order to control potential confounding effects data were also collected from cases and controls with respect to schooling years of the woman and her husband, place of residence (urban or rural) before permanent settlement in Athens (all women were permanent residents of Athens) and occupation (housewife, other). Analysis was done with standard stratification procedures [8, 9].

Results

Table 1 shows univariate characteristics of cases and controls with respect to age in years, woman's schooling in years, husband's schooling in years, previous

residence (rural, i.e. less than 10000, or urban) and woman's occupation (housewife or other). There are clearly no significant differences with respect to woman's schooling, husband's schooling and previous residence, but age and woman's occupation are potential confounders and should be controlled in the analysis.

Tab. 1. Univariate characteristics of 103 non-smoking ever-married women, first hospitalized with chronic obstructive pulmonary disease, and 179 non-smoking ever-married visitor controls, with respect to potential confounding factors

Risk factors	COPD		Controls		Difference or heterogeneity (P two tails)
	N	%	N	%	
Age (years)					
40-49	21	20.4	44	24.6	
50-59	22	21.4	67	37.4	
60-69	26	25.2	50	27.9	0.001
70-79	34	33.0	18	10.1	
Woman's schooling					
-5	56	54.4	92	51.4	
6+	47	45.6	87	48.6	0.6
Husband's schooling					
-5	34	33.0	52	29.1	
6+	69	67.0	127	70.9	0.5
Previous residence					
Rural	41	39.8	62	34.6	
Urban	62	60.2	117	65.4	0.4
Woman's occupation					
Housewife	55	53.4	123	68.7	
Other	48	46.6	56	31.3	0.01

Tab. 2. Distribution of 103 non-smoking ever-married women, first hospitalized with chronic obstructive pulmonary disease, and 179 non-smoking ever-married visitor controls, by age, occupation and average daily number of cigarettes smoked by the husband

Age	Occupation	Cases or Controls	Average daily number of cigarettes smoked by the husband				Total
			Non-smoking	ex-smoker	1-20	21+	
40-49	Housewife	Cases	0	1	8	5	14
		Controls	9	5	3	13	30
40-49	Working	Cases	1	1	0	5	7
		Controls	2	3	3	6	14
50-59	Housewife	Cases	3	1	5	0	9
		Controls	7	14	13	16	50
50-59	Working	Cases	1	1	4	7	13
		Controls	7	2	3	5	17
60-69	Housewife	Cases	2	1	5	5	13
		Controls	3	13	6	9	31
60-69	Working	Cases	2	2	4	5	13
		Controls	2	10	2	5	19
70-79	Housewife	Cases	3	7	7	2	19
		Controls	1	3	3	5	12
70-79	Working	Cases	1	4	2	8	15
		Controls	2	2	1	1	6
Total		Cases	13	18	35	37	103
		Controls	33	52	34	60	179
Relative risk (crude)			1.0	0.9	2.6	1.6	
Relative risk (Mantel-Haenszel)			1.0	0.6	2.4	1.4	
(90% Confidence Limits)				0.3-1.3	1.3-4.5	0.8-2.6	
χ^2 for trend, crude = 3.57			P one tail = 0.03				
χ^2 for trend, Mantel extension = 3.80			P one tail = 0.03				

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Tab. 3. Distribution of 103 non-smoking ever-married women, first hospitalized with chronic obstructive pulmonary disease, and 179 non-smoking ever-married visitor controls, by age, occupation and total life-long number of cigarettes smoked by the husband (in thousands)

Age	Occupation	Cases or Controls	Life-long total number of cigarettes smoked by the husband (thousands)			
			non-smoker	< 300	> 300	Total
40-49	Housewife	Cases	0	13	1	14
		Controls	9	14	7	30
40-49	Working	Cases	1	5	1	7
		Controls	2	11	1	14
50-59	Housewife	Cases	3	5	1	9
		Controls	7	32	11	50
50-59	Working	Cases	1	7	5	13
		Controls	7	6	4	17
60-69	Housewife	Cases	2	3	8	13
		Controls	3	19	9	31
60-69	Working	Cases	2	5	6	13
		Controls	2	11	6	19
70-79	Housewife	Cases	3	9	7	19
		Controls	1	10	1	12
70-79	Working	Cases	1	5	9	15
		Controls	2	1	3	6
Total		Cases	13	52	38	103
		Controls	33	104	42	179
Relative risk (crude)			1.0	1.3	2.3	
Relative risk (adjusted)			1.0	1.3	1.8	
(90% Confidence Limits)				0.8-2.4	0.9-3.6	
χ^2 for trend: crude = 5.58			P one tail = 0.01			
χ^2 for trend: Mantel extension = 3.44			P one tail = 0.03			

Tables 2 and 3 show the distributions of cases and controls by age, occupation and average daily number of cigarettes smoked by the husband (table 2), or total life-long number of cigarettes smoked by the husband in thousands (table 3). In both instances there are statistically significant (one tail $P < 0.05$) linear trends between amount of tobacco smoked by the husband and risk of (hospitalization for) COPD. Thus, it appears that exposure to environmental tobacco smoke may contribute to the development of COPD with an associated relative risk of about 2.

Discussion

Many epidemiologic investigations have firmly established that exposure of children to environmental tobacco smoke, usually attributable to the smoking habits of their parents, has clear effects on their respiratory system. The relevant studies, more than 25 by now, have recently been reviewed [6, 7, 10, 11]. By contrast, studies in adults have been fewer and their results less clear-cut. Most of these studies have focused on pulmonary function rather than on clinical syndromes, and among them about half have found significant evidence that exposure to environmental tobacco smoke has adverse pulmonary effects [12-16], whereas in the other half such evidence was not apparent [17-21].

Very few studies have examined the association, if any, between exposure to environmental tobacco smoke and development of COPD as a clinical entity - for instance no such study has been included in the

major review volumes published by the National Research Council [7] and the Surgeon General [6] or the recent review paper by Fielding and Phenow [11]. Yet investigations of a possible link between exposure to ETS and chronic obstructive pulmonary disease should be particularly promising for at least three reasons: chronic obstructive pulmonary disease is one of the entities most strongly related to active smoking [3]; a clinical COPD is by definition an extreme expression of the pathophysiological changes manifested as disturbances of pulmonary function(s) and it is a general epidemiologic principal that «extreme points» designs are inherently more powerful [22]; since individuals more susceptible to the irritating effects of cigarette smoke on the lower respiratory tract are more likely to be non-smokers [7], a population of non-smokers passively exposed to ETS would be more likely to include susceptible individuals, who in turn would be more likely to develop the constellation of symptoms and signs of COPD.

There are in the literature short reports of, or references to, three studies concerning the association between passive smoking and COPD. In the cohort study of Hirayama in Japan, a statistically significant relative risk of 1.6 was found in non-smoking women passively exposed to the tobacco smoke of their husband [23]. In papers presented in 1987 in the meetings of the Society for Epidemiologic Research and the International Epidemiology Association, Sandler and her colleagues reported that in their cohort an increased relative mortality from respiratory diseases

was found among non-smokers passively exposed to tobacco smoke, compared to non-smokers not so exposed [24]. There has been also a brief publication of preliminary results of the present study [5] (there are slight differences between the figures reported earlier and those shown here, due to recoding and use of different strata in the standardization procedures). The results of the present study taken together with those of the two cohort studies [23, 24] and the collective findings of the epidemiologic studies exploring the association between exposure to ETS and various parameters of pulmonary function, suggest that passive smoking may contribute to the development of COPD. The reported association is unlikely to be explained in terms of misclassification of current or past smokers as non-smokers [25]. Furthermore, relative risk figures generated from empirical studies should be adjusted upwards, since few, if any, subjects are actually completely unexposed to passive smoking [26]. Lastly, random misclassification of ETS exposure and misspecification of biologic latency are likely to generate systematic underestimation of the true underlying relative risk.

Summary

One hundred and three ever-married women with newly diagnosed Chronic Obstructive Pulmonary Disease (COPD), who have never smoked, and 179 ever-married women who were visiting friends or relatives at the same hospital during the same period and have never smoked, were interviewed regarding the smoking habits of their husbands. There was statistically marginally significant difference between the COPD cases and the controls with respect to their husband's smoking habits. The association was irregular with respect to daily number of cigarettes smoked but there was a smooth dose response curve with respect to life long total number of cigarettes smoked, with women whose husband smoked more than 300 thousand cigarettes having a relative risk of 1.8 (90% confidence interval of 0.9-3.6) compared to women whose husband has never smoked. These findings, and converging related evidence, indicate that exposure to environmental tobacco smoke may be a risk factor for the development of COPD.

Résumé

Effets de la fumée passive sur la survenue d'un syndrome broncho-obstructif chronique

Cent-trois femmes, mariées de longue date, n'ayant jamais fumé, et chez qui un syndrome broncho-obstructif chronique (SOC) a été récemment diagnostiqué, ont été interrogées pour ce qui concerne les habitudes tabagiques de leur mari. Leurs réponses furent comparées à celles de 179 femmes, également mariées de longue date et non-fumeuses, qui s'étaient rendues dans le même hôpital pour rendre visite à un parent ou ami. Les habitudes tabagiques des maris sont différentes entre les cas de SOC et les contrôles, mais les différences ne sont que marginalement statistiquement significatives. L'association est inconstante par rapport au nombre quotidien de cigarettes fumées, cependant la courbe dose-réponse en fonction du nombre total de cigarettes fumées au cours de la vie montre une progression régulière. Les femmes dont les maris ont fumé plus de 300 000 cigarettes ont un risque relatif de développer un SOC de 1.8 (intervalle de confiance 90%: 0.9-3.6) par rapport aux femmes dont les maris n'ont jamais fumé. L'association décrite ici, ainsi que d'autres preuves concordantes, indiquent que l'exposition passive à la fumée de cigarettes peut être un facteur de risque pour la survenue du SOC.

Zusammenfassung

Passivrauchen und chronisch obstruktive Lungenerkrankheiten

In einer Fall-Kontroll-Studie wurden 103 Patientinnen mit chronisch obstruktiver Lungenerkrankheit erfasst, die nie geraucht hatten und zur Zeit der Studie verheiratet waren oder es zumindest früher einmal gewesen waren. Als Kontrollen dienten 179 Frauen auf Krankenvsiten im selben Spital, die ebenfalls nie geraucht hatten und auch zumindest einmal verheiratet gewesen waren. Verglichen wurden die Rauchgewohnheiten der Ehemänner. Der einfache Vergleich Raucher-Nichtraucher ergab eine schwach signifikante Differenz, ein eindeutiger Zusammenhang mit der täglich gerauchten Anzahl Zigaretten fand sich jedoch nicht. Eine dosisabhängige Beziehung zeigte sich bei der im Leben insgesamt gerauchten Anzahl Zigaretten: das relative Risiko war für Frauen, deren Ehemänner mehr als 300 000 Zigaretten geraucht hatten 1.8 im Vergleich zu Partnerinnen von Nichtrauchern (90% Vertrauensintervall 0.9-3.6). Diese Resultate konnten ein Hinweis dafür sein, dass Nichtrauchen ein Risikofaktor für chronisch obstruktive Lungenerkrankheiten sein könnte.

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